Parasympathetic Nervous System
Part I
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Autonomic Nervous System

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

Neurons of the ANS

Key Points
Preganglionic fibers – mylinated
Postganglionic fibers – non mylinated
SNS pre : post 1:20
PNS pre : post 1:1
(exception 1:10,000 Auerbachs plexus)
Key role of Ach
Motor fiber not part of ANS

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
  - M15, M14 -PLC, M14, AC
  - G-protein coupled
- **Nicotinic** (ion channel)
  - pentamer, 5 subunits
  - α4 or α3 -ganglia, adrenal medulla (α3β1, α3β2)
  - α8 or α2 -skeletal muscle (infant α2β1γ, adult α2β1β7)
  - α subunit, Ach binding (2)

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)

True Acetylcholinesterase (AchE)

(Other: 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>Circul*</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 Stimulants

Cholinergic Stimulants

Wild Mushrooms - Amanita

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)
  - Neostigmine (0.5-2 hr)

Myasthenia gravis

Autoimmune disease

- 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
- Neostigmine undergoes metabolism
- Enzyme becomes operational again
Irreversible inhibitors

- Organophosphates (highly lipid soluble, >50,000 compounds)
  - Diisopropyl-fluorophosphate (DFP)
  - Echotoxiphate (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-PM 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)
    - Phystostigmine 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)
  - Phystostigmine is preferred (CNS action)

Actions on the Eye

Glaucoma 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

Acetylcholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Uses</th>
<th>Approximate Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohols</td>
<td></td>
</tr>
<tr>
<td>Carbamates 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 i.e. Atropine
  - AchE reactivator (Pralidoxime, 2-PAM)
  - Mechanical respiration

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### Symptoms of Parasympathetic Toxicity

<table>
<thead>
<tr>
<th>SLUDGE</th>
<th>DUMBBELLS</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>
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</tr>
</tbody>
</table>

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### Neurons of the ANS

[Diagram showing neurons of the ANS]