Pharmacology of the Parasympathetic Nervous System

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Autonomic Nervous System

Key Points
- 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

Cholinoreceptors

Cholinergic Neurotransmission

Rate limiting step
Uptake of choline into nerve terminal

Termination
Enzymatic by acetylcholinesterase (AchE)
Cholinergic Receptors

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

- **Nicotinic** (ion channel)
  - pentamer, 5 subunits
  - N1 or N2: ganglia, adrenal medulla (α2β3, α3β2)
  - N3 or N4: skeletal muscle (infant α1β1δε, adult α2βδγ)
  - 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)
  - 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 emergence)
  - 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>
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<tr>
<th>AchE</th>
<th>BuChE</th>
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<td>Nerves</td>
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<td>NMJ</td>
<td>Yes</td>
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<tr>
<td>Circ.</td>
<td>Little</td>
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Quaternary group Acyl carbon

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

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 (e.g., physostigmine)
  - Irreversible inhibitors (e.g., 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
- Widened 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 0.15 msec
- Neostigmine undergoes metabolism 0.5-6 hr
- Enzyme becomes operational again
Irreversible inhibitors

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

**Acetylcholinesterase & Irreversible Inhibition**

DFP, Isoflurophate

\[
\text{P}_3 \text{O} \quad \text{R}_1 \quad \text{X}
\]

2-PAM

Pralidoxime

No CNS action

DFP Aging

30-40 min

Nerve gas

secs / 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 echthiophate (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**

Glaucoma treatment

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

**Acetylcholinesterase Inhibitors**

<table>
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<tr>
<th>Drugs</th>
<th>Uses</th>
<th>Approximate Duration of Action</th>
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<tr>
<td>Alcohols</td>
<td>Edrophonium (Tensilon) Myasthenia gravis, ileus, arrhythmias</td>
<td>5-15 minutes</td>
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<tr>
<td>Carbamates and related agents</td>
<td>Neostigmine (Prostigmine) Myasthenia gravis, ileus</td>
<td>1/2-2 hours</td>
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<tr>
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<td>Pyridostigmine (Mestinon) Myasthenia gravis</td>
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<td>Physostigmine (Eserine) Glaucoma</td>
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<td>Ambenonium (Mytelase) Myasthenia gravis</td>
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<td>Demecarium (Humorsol) Glaucoma</td>
<td>4-6 hours</td>
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<tr>
<td>Organophosphates</td>
<td>Echothiophate, DFP (Phospholine), etc. Glaucoma</td>
<td>100 hours</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

Toxicity of AchE Inhibitors

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<tr>
<th>SLUDGE</th>
<th>DUMBBELS</th>
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<tr>
<td>S - Salivation</td>
<td>D - Diarrhea</td>
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<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>
<tr>
<td></td>
<td>L - Lacrimation</td>
</tr>
<tr>
<td></td>
<td>S - Salivation/sweating</td>
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Parasympatholytic Agents

- **Antimuscarinic:** eg. atropine
  - block Ach in parasympathetic effector junctions (muscarinic receptors)

- **Antinicotinic: Ganglia** eg. mecamylamine
  - block Ach in ganglia (both parasympathetic and sympathetic, N1 or N2-receptors)

- **Antinicotinic: NMJ** eg. curare, succinylcholine
  - block Ach in neuromuscular junctions (skeletal muscle relaxants, N2 or N2-receptors)

Antimuscarinic Agents

- **Belladonna alkaloids:** well absorbed, CNS effects
  - atropine (7-10 d) - “belladonna”
  - homatropine (1-3 d) - iritis
  - scopolamine (3-7 d) - motion sickness

- **Synthetic antimuscarinics**
  - ipratropium (quaternary amine) - asthma
  - pirenzepine (tri-cyclic, M1-selective) - ulcer
  - benztropine - Parkinson’s disease
  - glycopyrolate (quaternary amine)
  - cyclopentolate (tertiary amine)
  - propantheline (quaternary amine)

Anticholinergic Effects on Organ Systems

- **Heart:** tachycardia, ↑ A-V nodal CV (M2-receptors)
- **Vasculature:** no effect, although toxic doses cause pronounced vasodilation (red blotches)
- **Smooth muscle**
  - GI-tract, urinary tract: relaxation, ↓ secretion, ↓ motility
  - Lung: bronchial relaxation & ↓ bronchial secretions
  - Eye: mydriatic (sphincter relaxation), cyclopegic (ciliary muscle relaxation)
- **Secretions**
  - ↓ secretion: dry mouth, dry skin,
  - ↓ decreased gastric acid secretion
- **CNS:** agitation, delirium, confusion, elderly are more susceptible

Deadly Nightshade

- Approx 5,000 per yr

- Mainly atropine
- Devil’s apple
- Stink weed
- Devil’s cherries

Datura

- Mainly scopolamine & hyoscyamine
- Thorn apple
- Jimson weed
Other Parasympatholytics

Hemicholinium
- no clinical use
- inhibits uptake of choline into nerve terminal (rate limiting step)
- leads to decreased Ach synthesis

Botulinus toxin
- prevent release of Ach
- contamination of improperly prepared food

Clinical use: facial muscle spasms, strabismus, wrinkles

Clinical uses of Antimuscarinic Agents

- respiratory (decrease bronchial secretion) ie. atropine
- asthma ie. ipratropium
- ophthalmologic (mydriasis, cycloplegia) ie. iritis
- Parkinson's disease ie. benztrapine
- cardiovascular ie. atropine
- motion sickness ie. scopolamine
- GI disorders (peptic ulcers (pirenzepine), diarrhea)
- pesticide poisoning (malathion) ie. atropine
- nerve gases (sar) ie. atropine + 2-PAM

Toxicity and treatment

- Toxicity:
  dry mouth, mydriasis, tachycardia, hot flushed skin, agitation and delirium.
  High concentrations may cause ganglionic-blockade leading to hypotension

- Treatment:
  - quaternary cholinesterase inhibitor eg. neostigmine or physostigmine (cns action)
  - for hypotension: sympathomimetics (α-agonist, eg. methoxamine)

Symptoms of Antimuscarinic Toxicity

Belladonna (beautiful lady) poisoning

- mad as a hatter: CNS, delirium
- red as a beet: direct vasodilation
- blind as a bat: cycloplegia
- hot as hell (a hare): ↓sweat, thermoregulation
- dry as a bone: decreased secretions

Mad as a Hatter

Mercury was used to treat hats. It was applied on to the fur to roughen the fibres and make them mat more easily

Mercury is a cumulative poison that causes kidney and brain damage. Physical symptoms include trembling (known at the time as hatter's shakes), loosening of teeth, loss of co-ordination, and slurred speech; mental ones include irritability, loss of memory, depression, anxiety, and other personality changes. This was called mad hatter syndrome.
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<th><strong>Type</strong></th>
<th><strong>Members</strong></th>
<th><strong>Effects</strong></th>
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<tr>
<td>Agonists</td>
<td>1. Ach</td>
<td>1. heart: bradycardia, decreased contractility, decreased conduction velocity in the AV node</td>
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<tr>
<td></td>
<td>2. Bethanecol</td>
<td>2. vasculature: mediate vasodilation via synthesis of NO by endothelial cells</td>
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<td>4. Methacholine</td>
<td>4. eye: contraction of sphincter (miosis) &amp; ciliary muscle for near vision</td>
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<td>5. exocrine glands: sweating (SNS), salivation &amp; gastric acid secretion</td>
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<td>1. atropine</td>
<td>non-selective, long lasting</td>
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<td>2. scopolamine</td>
<td>centrally acting</td>
<td></td>
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<tr>
<td>3. homatropine</td>
<td>shorter acting</td>
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<td>4. pirenzepine</td>
<td>M1 receptor selective (anti-ulcer)</td>
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