Parasympathetic Nervous System
Part II

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Parasympatholytic Agents

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

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

- **Antinicotinic: NMJ** eg. curare, succinylcholine
  - block Ach in neuromuscular junctions (skeletal muscle relaxants, N0 or N2-receptors)

Anticholinergic Effects on Organ Systems

- **Heart:** tachycardia, ↑ A-V nodal CV (M2-receptors)
- **Vasculature:** no effect, although toxic doses cause pronounced direct 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

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, COPD
  - tiotropium - COPD
  - pirenzepine (tri-cyclic, M1-selective) - ulcer
  - benztropine - Parkinson’s disease
  - glycopyrolate (quaternary amine)
  - cyclopentolate (tertiary amine)
  - propantheline (quaternary amine)

Deadly Nightshade

Approx 5,000 per yr

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

Datura

Mainly scopolamine & hyoscyamine

Mainly from

- Thorn apple
- Jimson weed

Chronic Obstructive Pulmonary Disease (COPD)

- Damage to lungs
- Develops slowly
- No cure
- 4th US Cause of death
- Smoking common cause

Treatment (inhaled):
- Beta2-agonists
- M-receptor blockers (ipratropium, tiotropium)
- Glucocorticosteroids
- Oxygen
Clinical uses of Antimuscarinic Agents

- respiratory (decrease bronchial secretion) ie. atropine
- Asthma, COPD ie. ipratropium, tiotropium
- ophthalmologic (mydriasis, cycloplegia) eg. iritis (ie. atropine)
- Parkinson's disease ie. benztropine
- cardiovascular ie. atropine
- motion sickness ie. scopolamine
- GI disorders (peptic ulcers (pirenzepine), diarrhea)
- Rx pesticide poisoning (malathion) ie. atropine + 2-PAM
- Rx mushroom poisoning (muscarine) ie. atropine
- Rx nerve gases (Vx, sarin) ie. atropine + 2-PAM

Toxicity and treatment

- **Toxicity:**
  - dry mouth, mydriasis, cycloplegia, 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)

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 (blepharospasm, eye twitching or eye spasm) strabismus, wrinkles

Botulinum toxin

*Inhibits Ach release*
*Single treatment can last 3-4 months*

Facial wrinkles, FDA Approval: Apr 2002

**Toxicity:**
- 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

Belladonna (beautiful lady)
Pharmacology of the Eye

“The eye is a good example of an organ with multiple ANS functions, controlled by several different autonomic receptors.” (Katzung)

Increased intraocular pressure: Untreated → blindness

Glucoma:
- Open-angle (wide, chronic) – treated with beta-blockers and other agents
- Closed-angle (narrow-angle) – dilated iris can occlude outflow. Pilocarpine or surgical removal of part of iris (iridectomy)

Ach effects on smooth muscle in the eye

Contraction of sphincter muscle → miosis
Contraction of ciliary muscle for near vision

Glaucoma:
- Open angle (wide, chronic) – treated with beta-blockers and other agents
- Closed angle (narrow-angle) – dilated iris can occlude outflow
- Pilocarpine or surgical removal of part of iris (iridectomy)

Actions on the Eye

Glaucoma treatment

1. $\alpha$-Agonist: ↑Outflow
2. M-Agonists/AchEI: ↑Outflow
3. $\beta$-Blocker: ↓Secretion
4. $\alpha_2$-Agonist: ↓Secretion
5. Prostaglandins: ↑Outflow
6. Carbonic acid inhibitors: ↓Secretion

Open Angle vs Closed Angle Glaucoma

Prostaglandin analogues
(Latanoprost, Bimatoprost, Travoprost, Unoprostone)

Side effects:
- darkening of the iris
- lengthening and thickening of eyelashes
- intraocular inflammation
Drugs used in glaucoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinomimetics</td>
<td>Pilocarpine (acute DOC),</td>
<td>Ciliary muscle contraction → opening of trabecular meshwork → ↑ outflow</td>
</tr>
<tr>
<td>Alpha Agonists</td>
<td>Unselective: Epinephrine,</td>
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<tr>
<td>Alpha2-Selective Agonists</td>
<td>Apraclonidine, Brimonidine</td>
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<tr>
<td>Beta-Blockers</td>
<td>Timolol, betaxolol, carteolol</td>
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<tr>
<td>Diuretics</td>
<td>Carbonic acid inhibit.</td>
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<tr>
<td>Topical Diuretics</td>
<td>Acetazolamide, Methazolamide</td>
<td></td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Latanoprost, Bimatoprost</td>
<td></td>
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</tbody>
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**Clinical Setting**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pupillary Response</th>
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</thead>
<tbody>
<tr>
<td>Normal Alpha agonist</td>
<td>ls. phenylephrine</td>
</tr>
<tr>
<td>Normal Muscarinic agonist</td>
<td>ls. pilocarpine</td>
</tr>
<tr>
<td>Normal Muscarinic antagonist ls. atropine</td>
<td>Mydriasis, cycloplegia</td>
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<tr>
<td>Horner’s syndrome</td>
<td>Cocaine</td>
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<tr>
<td>Preganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
</tr>
<tr>
<td>Postganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
</tr>
<tr>
<td>Adie’s pupil</td>
<td>Pilocarpine</td>
</tr>
<tr>
<td>Normal Opioids (oral or intravenous)</td>
<td>Pinpoint pupils</td>
</tr>
</tbody>
</table>

**Parasympathetic Summary**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Agonists</td>
<td>1. Ach</td>
</tr>
<tr>
<td></td>
<td>2. Bethaneol</td>
</tr>
<tr>
<td></td>
<td>3. Pilocarpine</td>
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<tr>
<td></td>
<td>4. Methacholine</td>
</tr>
<tr>
<td>Antagonists</td>
<td>1. atropine - non-selective, long lasting</td>
</tr>
<tr>
<td></td>
<td>2. acamolamine – CNS</td>
</tr>
<tr>
<td></td>
<td>3. homatropine – shorter acting</td>
</tr>
<tr>
<td></td>
<td>4. propranolol - asthma</td>
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<tr>
<td></td>
<td>5. prterpine - M1 receptor selective (ulcro)</td>
</tr>
<tr>
<td>Agonists</td>
<td>1. heart ⇒ bradyarrhythmia, ↓ heart rate, ↓ conduction velocity in the AV node</td>
</tr>
<tr>
<td></td>
<td>2. vasculature ⇒ mediate vasodilatation via synthesis of NO by endothelial cells</td>
</tr>
<tr>
<td></td>
<td>3. smooth muscle ⇒ ↑ tone in intestine &amp; bladder, ↓ tone in intestines &amp; bladders</td>
</tr>
<tr>
<td>Antagonists</td>
<td>1. heart ⇒ tachycardia, ↓ heart rate, ↓ conduction velocity in the AV node</td>
</tr>
<tr>
<td></td>
<td>2. vasculature ⇒ no effect (no cholinergic innervation)</td>
</tr>
<tr>
<td></td>
<td>3. smooth muscle ⇒ relaxation in GI &amp; urinary bladder</td>
</tr>
<tr>
<td></td>
<td>4. eye ⇒ mydriasis &amp; cycloplegia</td>
</tr>
<tr>
<td></td>
<td>5. exocrine glands ⇒ ↑ sweating (SNS), salivation &amp; gastric acid secretion</td>
</tr>
</tbody>
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**Acetylcholinesterase Inhibitors**

<table>
<thead>
<tr>
<th>Type</th>
<th>Agents</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly reversible (competitive)</td>
<td>Edrophonium ⇒ used for myasthenia gravis (aka Tension)</td>
<td></td>
</tr>
<tr>
<td>Slowly reversible (competing substrate, carbyamylates enzyme)</td>
<td>1. Neostigmine ⇒ does not cross BBB; affects skeletal muscle most strongly; used for myasthenia gravis &amp; luteus</td>
<td></td>
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<tr>
<td></td>
<td>2. Physostigmine ⇒ crosses BBB, used for glaucoma and for treatment of belladonna poisoning</td>
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<tr>
<td></td>
<td>3. Pyridostigmine ⇒ used for myasthenia gravis</td>
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<td></td>
<td>4. Ambenonium ⇒ used for myasthenia gravis</td>
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<td></td>
<td>5. Demecarium ⇒ used for glaucoma</td>
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<tr>
<td>Irreversible or very slowly reversible (phosphorylates enzyme)</td>
<td>Organophosphate insecticides, nerve gases</td>
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<tr>
<td>Echotoxiphate ⇒ used for glaucoma</td>
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</tbody>
</table>

**Question 3**

The circles represent the size of the pupils of a patient's right and left eyes, both without treatment and with two different treatments. Which of the following is compatible with the findings shown for the left eye?

A. Blockade of α-adrenergic rec.  
B. Blockade of β-adrenergic rec.  
C. Blockade of muscarinic rec.  
D. Inhibition of cholinesterase  
E. Sympathetic denervation

**Eye - Horner's Syndrome**

Destruction of Sympathetic innervation to the iris
- loss of preganglionic fibers
- loss of postganglionic fibers
- parasympathetic innervation left unopposed

Horner's Syndrome (note sagging left eyelid and miosis)