Parasympathetic Nervous System
Part II

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Neurons of the ANS
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, $N_N$ or $N_1$-receptors)

• **Antinicotinic: NMJ** eg. curare, succinylcholine  
  - block Ach in neuromuscular junctions (skeletal muscle  
    relaxants, $N_M$ or $N_2$-receptors)

Anticholinergic Effects on Organ Systems

• **Heart**: tachycardia, $\uparrow$ 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, $\downarrow$ secretion, $\downarrow$ motility  
  - Lung: bronchial relaxation & $\downarrow$ bronchial secretions  
  - Eye: mydriatic (sphincter relaxation), cyclopegic (ciliary  
    muscle relaxation)

• **Secretions**  
  - $\downarrow$ secretion: dry mouth, dry skin,  
  - $\downarrow$ 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)

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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
Virginia Beach Officials Investigate Rash of Jimsonweed Poisonings - Jan 2006

- 12 teenagers were diagnosed with Jimsonweed poisonings
- Jimsonweed, also known as thorn apple, stinkweed, and Jamestown weed
- it is sometimes eaten - or made into a tea - and ingested in an attempt to get high
- they displayed symptoms such as combative behavior, dry mouth/thirst, blurred vision hallucinations and elevated body temperature

Chronic Obstructive Pulmonary Disease (COPD)

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

Treatment (inhaled):
- Beta2-agonists
- M-receptor blockers
- Glucocorticosteroids
- Oxygen
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

Before

After

Facial wrinkles, FDA Approval: Apr 2002
Botulinum toxin - Strabismus

Botulinum toxin – Blepharospasm
(Eye twitching, eye spasm)
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)
Antimuscarinic Toxicity

Belladonna (beautiful lady)

- 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

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

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)
Glaucoma

Increased intraocular pressure: Untreated → blindness

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)

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

Innervation of the iris

[Diagram showing innervation of the iris with labels and pathways]
Ach effects on smooth muscle in the eye

**Contraction of sphincter muscle** → miosis

**Contraction of ciliary muscle for near vision**

Actions on the Eye

**Glaucoma treatment**

1. α-Agonist
   ↑Outflow

2. M-Agonists
   ↑Outflow

3. β-Blocker
   ↓Secretion

4. α2-Agonist
   ↓Secretion

5. Prostaglandins
   ↑Outflow

6. Carbonic acid inhibitors
   ↓Secretion
Drugs used in glaucoma

<table>
<thead>
<tr>
<th>Cholinomimetics</th>
<th>Ciliary muscle contraction → opening of trabecular meshwork → ↑ outflow</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine, physostigmine, echothiophate</td>
<td></td>
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</table>

的效果

<table>
<thead>
<tr>
<th>Alpha Agonists: Unselective: Epinephrine</th>
<th>↑ Outflow</th>
<th>Tropical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha2-Selective Agonists: Apraclonidine</td>
<td>↓ Aqueous secretion from the ciliary epithelium</td>
<td>Topical</td>
</tr>
<tr>
<td>Beta-Blockers: Timolol, betaxolol, carteolol</td>
<td>↓ Aqueous secretion from the ciliary epithelium</td>
<td>Topical</td>
</tr>
<tr>
<td>Diuretics: Carbonic acid inhib. Acetazolamide, Methazolamide Dorzolamide, Brinzolamide</td>
<td>↓ Secretion due to lack of HCO₃⁻</td>
<td>Oral Topical</td>
</tr>
<tr>
<td>Prostaglandins: Latanoprost (PGF₂α)</td>
<td>↑ Outflow</td>
<td>Topical</td>
</tr>
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Effects of pharmacological agents on the pupil

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Drug</th>
<th>Pupillary Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Alpha agonist ie. phenylephrine</td>
<td>Dilation (mydriasis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Muscarinic agonist ie. pilocarpine</td>
<td>Constriction (miosis) cycloplegia</td>
</tr>
<tr>
<td>Normal</td>
<td>Muscarinic antagonist ie. atropine</td>
<td>Mydriasis, cycloplegia</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Cocaine</td>
<td>No dilation</td>
</tr>
<tr>
<td>Preganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>Dilation</td>
</tr>
<tr>
<td>Postganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>No dilation</td>
</tr>
<tr>
<td>Adie’s pupil</td>
<td>Pilocarpine</td>
<td>Constriction</td>
</tr>
<tr>
<td>Normal</td>
<td>Opioids (oral or intravenous)</td>
<td>Pinpoint pupils</td>
</tr>
</tbody>
</table>
Eye - Horners Syndrome

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

Horners Syndrome (note sagging left eyelid and miosis)

Adies Pupil & Iritis

Adies Pupil
Poor light reflex
Dilated pupil

Iritis
Muscarinic blocker to dilate pupil to prevent attachment to lens.
Steroid to treat inflammation.
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

Without treatment

Treatment With TYR

Treatment With EPI

Topical scopolamine drops on pupil diameter and accommodation. in the normal human eye. One drop (0.5%) at zero time and 30 min.
## Parasympathetic Summary

<table>
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<tr>
<th>Antagonists</th>
<th>Agents</th>
<th>Effects</th>
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<tr>
<td>1. Atropine - non-selective, long lasting</td>
<td>1. Heart $\Rightarrow$ bradycardia, $\downarrow$ contractility, $\downarrow$ conduction velocity in the AV node</td>
<td>1. Heart $\Rightarrow$ tachycardia, $\uparrow$ AV node conduction</td>
</tr>
<tr>
<td>2. Scopolamine – CNS</td>
<td>2. Vasculature $\Rightarrow$ vasodilation by endothelial cells</td>
<td>2. Vasculature $\Rightarrow$ no effect (no cholinergic innervation)</td>
</tr>
<tr>
<td>3. Homatropine – shorter acting</td>
<td>3. Smooth muscle $\Rightarrow$ $\uparrow$ tone in intestine &amp; bladder, $\downarrow$ tone in sphincters</td>
<td>3. Smooth muscle $\Rightarrow$ relaxation in GI &amp; urinary tract; $\uparrow$ tone in sphincters</td>
</tr>
<tr>
<td>4. Ipratropium - asthma</td>
<td>4. Eye $\Rightarrow$ contraction of pupil (miosis) &amp; ciliary muscle for near vision</td>
<td>4. Eye $\Rightarrow$ mydriasis &amp; cycloplegia</td>
</tr>
<tr>
<td>5. Pirenzepine - M1 receptor selective (ulcer)</td>
<td>5. Exocrine glands $\Rightarrow$ sweating (SNS), salivation &amp; gastric acid secretion</td>
<td>5. Exocrine glands $\Rightarrow$ $\uparrow$ sweating (SNS), salivation &amp; gastric acid secretion</td>
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## AcetylCholinesterase Inhibitors

| Rapidly reversible (competitive) | Edrophonium $\Rightarrow$ used for myasthenia gravis (aka Tensilon) |
| Slowly reversible (competing substrate, carbamylates enzyme) | 1. Neostigmine $\Rightarrow$ does not cross BBB; affects skeletal muscle most strongly; used for myasthenia gravis & ileus |
| | 2. Physostigmine $\Rightarrow$ crosses BBB, used for glaucoma and for treatment of belladonna poisoning |
| | 3. Pyridostigmine $\Rightarrow$ used for myasthenia gravis |
| | 4. Ambenonium $\Rightarrow$ used for myasthenia gravis |
| | 5. Demercarium $\Rightarrow$ used for glaucoma |

| Irreversible or very slowly reversible (phosphorylates enzyme) | Organophosphate insecticides, nerve gases |
| | Echothiophate $\Rightarrow$ used for glaucoma |