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, N\textsubscript{2} or N\textsubscript{1}-receptors)
- **Antinicotinic: NMJ** eg. curare, succinylcholine
  - block Ach in neuromuscular junctions (skeletal muscle relaxants, N\textsubscript{a} or N\textsubscript{2}-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), cycloplegic (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

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
  - glycopyrrolate (quaternary amine)
  - cyclopentolate (tertiary amine)
  - propantheline (quaternary amine)

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
Botulinum toxin
Inhibits Ach release
Single treatment can last 3-4 months

Facial wrinkles, FDA Approval: Apr 2002

Clinical uses of Antimuscarinic Agents
- respiratory (decrease bronchial secretion) ie. atropine
- asthma ie. ipratropium
- 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)
- pesticide poisoning (malathion) ie. atropine + 2-PAM
- mushroom poisoning (muscarine) ie. atropine
- nerve gases (sarin) ie. atropine + 2-PAM

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

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 ($\alpha$-agonist, eg.methoxamine)

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 $\rightarrow$ 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)

Botulinum toxin - Strabismus
**Glaucoma**

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- 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 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

**Actions on the Eye**

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**

- Sympathetic pathway
- Parasympathetic pathway
- Innervation of the iris

**Ach effects on smooth muscle in the eye**

Contraction of sphincter muscle → miosis

Contraction of ciliary muscle for near vision

**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>
<td>Tropical</td>
</tr>
<tr>
<td>Alpha Agonists: Unselective: Epinephrine</td>
<td>↓ Aqueous secretion from the ciliary epithelium</td>
<td>Topical</td>
</tr>
<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>↓ Secretion due to lack of HCO3-</td>
<td>Oral, Topical</td>
</tr>
<tr>
<td>Diuretics: Carbonic acid inhib.</td>
<td>Latanoprost (PGF2α)</td>
<td>↑ Outflow</td>
</tr>
</tbody>
</table>

**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>Sympathomimetic ie. phenylephrine</td>
<td>Dilation (mydriasis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Parasympathomimetic ie. pilocarpine</td>
<td>Constriction (miosis) cyclopegia</td>
</tr>
<tr>
<td>Normal</td>
<td>Parasympatholytic ie. atropine</td>
<td>Mydriasis, cyclopegia</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Cocaine 4-10%</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 0.05-0.1%</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.

**Topical scopolamine drops on pupil diameter and accommodation.**

The normal human eye. One drop (0.5%) at zero time and 30 min.

- Pupil diameter
- Accommodation

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accommodation</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pupil Diameter</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

**Acetylcholinesterase Inhibitors**

<table>
<thead>
<tr>
<th>Neurons of the ANS</th>
<th>Edrophonium</th>
<th>Neostigmine</th>
<th>Physostigmine</th>
<th>Pyridostigmine</th>
<th>Demercarium</th>
<th>Ambenonium</th>
<th>Echothiophate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasympathetic</td>
<td>apricot</td>
<td>egg</td>
<td>mushroom</td>
<td>orange</td>
<td>potato</td>
<td>pineapple</td>
<td>plungers</td>
</tr>
<tr>
<td>Sympathetic</td>
<td>carrot</td>
<td>beet</td>
<td>banana</td>
<td>pear</td>
<td>potato</td>
<td>pineapple</td>
<td>carat</td>
</tr>
<tr>
<td>Somatic</td>
<td>cherry</td>
<td>beet</td>
<td>banana</td>
<td>pear</td>
<td>potato</td>
<td>pineapple</td>
<td>cherry</td>
</tr>
</tbody>
</table>

| Rapidly reversible (competitive) | Edrophonium | used for myasthenia gravis (aka Tensilon) |
| Slowly reversible (competing substrate, carbamylates enzyme) | Neostigmine | does not cross BBB; affects skeletal muscle most strongly; used for myasthenia gravis & lens |
| | Physostigmine | crosses BBB; used for glaucoma and for treatment of belladonna poisoning |
| | Pyridostigmine | used for myasthenia gravis |
| | Demecarium | used for myasthenia gravis |
| Irreversible or very slowly reversible (phosphorylates enzyme) | Organophosphate insecticides, nerve gases |
| | Edrophonium | used for glaucoma |
Structure and Physiology of the Autonomic Ganglion

- Ganglionic nicotinic (sympathetic & parasympathetic)
  - pentamer: 2 distinct subunits (α,β) - α2β3 or α3β2
  - α chains contain the Ach binding sites
  - binding of Ach → opening of ion channel (Na+ in, K+ out)

Ganglionic stimulants

- **Nicotine**
  - tobacco (0.3-20mg, fatal dose, 40mg)
  - metabolized & excreted rapidly
  - ↑ HR, ↑ BP, ↑ respiratory rate

- **Ach, DMPP** (experimental)

- **Lobeline** (tobacco)

- **Insecticides & rodenticide**
  - nicotine is often the effective agent

- **Toxicity**
  - CNS stimulation: convulsions, headache
  - NMJ paralysis: depolarizing blockade
  - hypertension, hypotension, cardiac arrhythmias
  - vomiting, diarrhea, salivation

Ganglionic Blocking Agents

- **Mecamylamine**
  - effective orally, CNS effects

- **Trimethapan**
  - inactive orally
  - used in hypertensive emergency (cns origin)
  - controlled hypotension during surgery
  - short duration of action, 5-10 min, no cns action

- **Toxicity**: hypotension, postural hypotension

- **Treatment**: pressor agent to counter hypotension

Treatment of poisoning from ganglionic stimulants

- **Treatment**:
  - vomiting induced for oral ingestion such as insecticides

- **Treatment symptom-directed**
  - muscarinic excess: anticholinergic (atropine)
  - NMJ blockade: mechanical respiration
  - CNS stimulation: anticonvulsant (diazepam)

Ganglionic Blocking Agents

<table>
<thead>
<tr>
<th>Site</th>
<th>Predominant ANS Effect</th>
<th>Effect of Ganglionic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioles</td>
<td>Sympathetic vasodilation, hypotension</td>
<td></td>
</tr>
<tr>
<td>Veins</td>
<td>Sympathetic vasodilation, ↓ venous return, ↓ CO</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Parasympathetic tachycardia</td>
<td></td>
</tr>
<tr>
<td>Iris</td>
<td>Parasympathetic mydriasis (dilation)</td>
<td></td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>Parasympathetic cycloplegia (loss of accommodation)</td>
<td></td>
</tr>
<tr>
<td>GI tract</td>
<td>Parasympathetic ↓ tone, ↓ motility, constipation</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>Parasympathetic urinary retention</td>
<td></td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Parasympathetic xerostomia (dry mouth)</td>
<td></td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Sympathetic anhidrosis (low sweating)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Ganglia block also high dose nicotine or high dose AchE inhibitors
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.