Parasympathetic Nervous System
Part II
Edward JN Ishac

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

Antinicotinic: Ganglia eg. trimethapan
- block Ach in ganglia (both parasympathetic and sympathetic, N_{2}O or N_{2}-receptors)

Antinicotinic: NMJ eg. curare, succinylcholine
- block Ach in neuromuscular junctions (skeletal muscle relaxants, N_{2}O or N_{2}-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 vasodilatation (red blots)
Smooth muscle
- GI-tract, urinary tract: relaxation, ↓ secretion, ↓ motility
- Lung: bronchial relaxation & ↓ bronchial secretions
- Eye: mydriastic (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

Botulinus toxin
- prevent release of Ach
- contamination of improperly prepared food
Clinical use: facial muscle spasms, strabismus, wrinkles

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

Inhibits Ach release
Single treatment can last 3-4 months

Before

After

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
- mushroom poisoning (muscarine) ie. atropine
- nerve gases (sarin) 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

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
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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

Ach effects on smooth muscle in the eye

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

Actions on the Eye

Cholinomimetics
Pilocarpine, physostigmine, echothiophate
Ciliary muscle contraction → opening of trabecular meshwork → ↑Outflow

Drugs used in glaucoma

- Cholinomimetics
  - Pilocarpine, physostigmine, echothiophate: ↑Outflow

- Alpha Agonists: Unselective: Epinephrine

- M-Agonists: Apraclonidine (↓Aqueous secretion from the ciliary epithelium)

- Beta-Blockers: Timolol, betaxolol, carteolol (↓Aqueous secretion from the ciliary epithelium)

- Diuretics: Carbonic acid inhib.: Dorzolamide, Brinzolamide (↑Outflow)

- Prostaglandins: Latanoprost (PGF2α) (↑Outflow)

Effects of pharmacological agents on the pupil

- Clinical Setting
- Drug
- Pupillary Response

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Drug</th>
<th>Pupillary Response</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Sympathomimetic is. phenylephrine</td>
<td>Dilatation (mydriasis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Parasympathomimetic is. pilocarpine</td>
<td>Constriction (miosis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Parasympatholytic is. atropine</td>
<td>Miosis, cycloplegia</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Cocaine 4-10%</td>
<td>Miosis, cycloplegia</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>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>
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</table>
Eye - Horner's 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 in the normal human eye. One drop (0.5%) at zero time and 30 min.

Parasympathetic Summary

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Antagonists</th>
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<tbody>
<tr>
<td>1. Ach</td>
<td>1. heart: bradycardia, ↓ conduction velocity of AV node, smooth muscle: ↓ tone in intestine &amp; bladder, ↓ tone in sphincters, eye: contraction of ciliary muscle; dilation of pupil &amp; dilatory muscle for near vision, exocrine glands: ↑ sweating (SNS), salivation, gastric acid secretion</td>
</tr>
<tr>
<td>2. Bethanecol</td>
<td>2. atropine - non-selective, long lasting</td>
</tr>
<tr>
<td>3. Pilocarpine</td>
<td>3. scopolamine – centrally acting</td>
</tr>
<tr>
<td>4. Methacholine</td>
<td>4. homatropine – shorter acting</td>
</tr>
</tbody>
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Acetylcholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Rapidly reversible (competitive)</th>
<th>Slowly reversible (competing substrate, carbamylates enzyme)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium: used for myasthenia gravis (aka Tensilon)</td>
<td>Neostigmine: does not cross BBB, affects skeletal muscle most strongly, used for myasthenia gravis &amp; f.e.</td>
</tr>
<tr>
<td>Physostigmine: cross BBB, used for glaucoma and for treatment of hallucinations</td>
<td>Physostigmine: no effect (no cholinergic innervation)</td>
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<tr>
<td>Pyridostigmine: shorter acting</td>
<td>Smooth muscle: relaxation in GI &amp; urinary tract</td>
</tr>
<tr>
<td>Homatropine: used for myasthenia gravis</td>
<td>Eye: mydriasis &amp; cycloplegia</td>
</tr>
<tr>
<td>Dibenamine: used for myasthenia gravis</td>
<td>Absorptive glands: dry mouth, dry skin, ↓ gastric acid secretion</td>
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Irreversible or very slowly reversible (phosphorylates enzyme)

Organophosphate esters, nerve gases
Edrophonium: used for glaucoma

Neurons of the ANS
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

Predominant autonomic nervous system on effector sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Predominant ANS</th>
<th>Effect of Ganglionic Blockade</th>
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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.