Parasympathetic Nervous System Part II

Edward JN Ishac

Smith Building, Room 742
eishac@hsc.vcu.edu
8-2127 8-2126

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

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, ↑ 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

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)

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

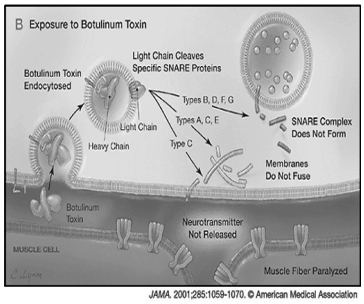
Botulinus toxin

- prevent release of Ach
- contamination of improperly prepared food

Clinical use: facial muscle spasms, strabismus, wrinkles

Botulinum toxin

Inhibits Ach release
Single treatment can last 3-4 months



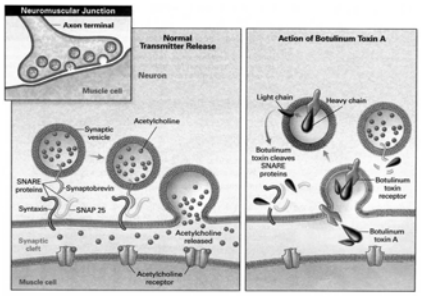
JAMA. 2001;285:1059-1070. © American Medical Association

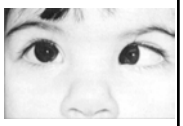
Before

After

Facial wrinkles, FDA Approval: Apr 2002

Botulinum toxin - Strabismus





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

Increased intraocular pressure: Untreated → blindness

Glaucoma:- Open angle (wide, chronic) – treated with beta-blockers and other agents
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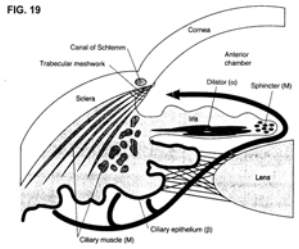
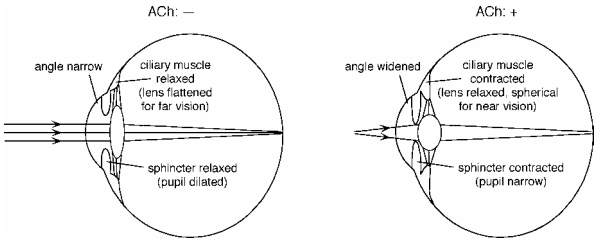


Glaucoma treatment
1. α-Agonist: ↑Outflow
2. M-Agonists: ↑Outflow
3. β-Blocker: ↓Secretion
4. α2-Agonist: ↓Secretion
5. Prostaglandins: ↑Outflow
6. Carbonic acid inhibitors: ↓Secretion

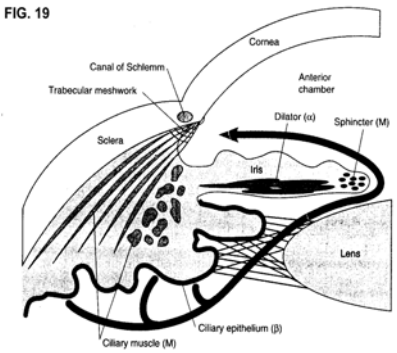
Ach effects on smooth muscle in the eye

Contraction of sphincter muscle → miosis

Contraction of ciliary muscle for near vision



Actions on the Eye



Glaucoma treatment

1. α-Agonist ↑Outflow

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3. β-Blocker ↓Secretion

4. α2-Agonist ↓Secretion

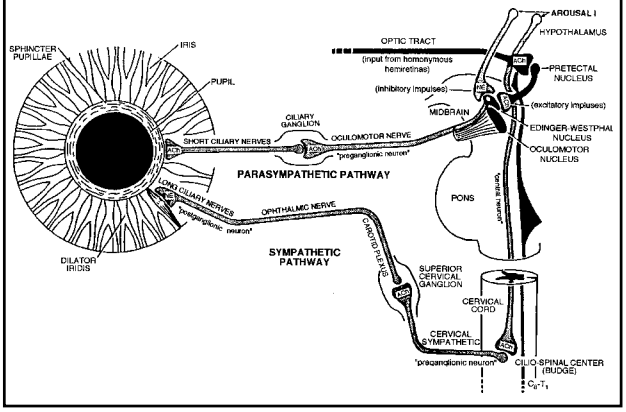
5. Prostaglandins ↑Outflow

6. Carbonic acid inhibitors ↓Secretion

Drugs used in glaucoma

Cholinomimetics Pilocarpine, physostigmine, echothiophate	**Ciliary muscule contraction → opening of trabecular meshwork → ↑outflow**	**Topical**
Alpha Agonists: Unselective: Epinephrine	**↑ Outflow**	**Tropical**
Alpha2-Selective Agonists: Apraclonidine	**↓ Aqueous secretion from the ciliary epithelium**	**Topical**
Beta-Blockers: Timolol, betaxolol, carteolol	**↓ Aqueous secretion from the ciliary epithelium**	**Topical**
Diuretics: Carbonic acid inhib. Acetazolamide, Methazolamide Dorzolamide, Brinzolamide	**↓ Secretion due to lack of HCO_3^-**	**Oral Topical**
Prostaglandins: Latanoprost (PGF2α)	**↑ Outflow**	**Topical**

Innervation of the iris



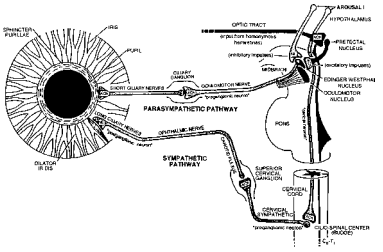
Effects of pharmacological agents on the pupil

Clinical Setting	Drug	Pupillary Response
Normal	**Sympathomimetic ie. phenylephrine**	**Dilation (mydriasis)**
Normal	**Parasympathomimetic ie. pilocarpine**	**Constriction (miosis) cyclopegia**
Normal	**Parasympatholytic ie. atropine**	**Mydriasis, cyclopegia**
Horner's syndrome	**Cocaine 4-10%**	**No dilation**
Preganglionic Horner's	**Hydroxyamphetamine**	**Dilation**
Postganglionic Horner's	**Hydroxyamphetamine**	**No dilation**
Adie's pupil	**Pilocarpine 0.05-0.1%**	**Constriction**
Normal	**Opioids (oral or intravenous)**	**Pinpoint pupils**

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

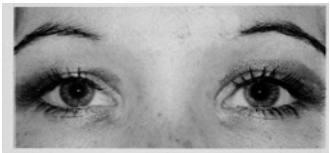
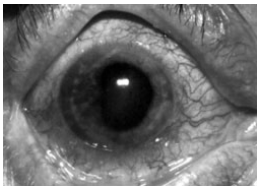


Fig. 12.9 Tonic pupil: the left pupil is dilated compared to the right.

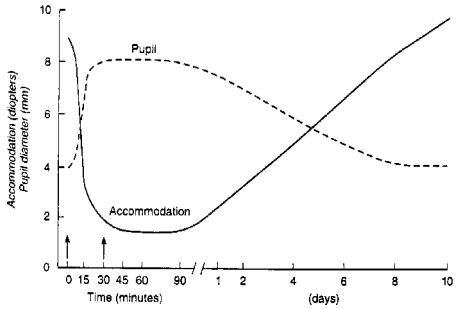
This 31 year old woman had been aware of pupillary asymmetry for some time. She presented with left facial numbness, the aetiology of which was not established. It rapidly resolved. Examination showed a typical left tonic pupil. The triceps and ankle jerks were depressed.

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.



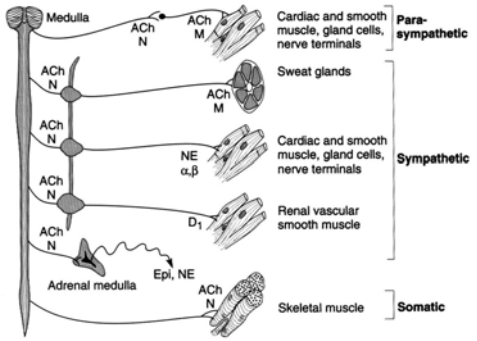
Parasympathetic Summary

	1. Ach 2. Bethanecol 3. Pilocarpine 4. Methacholine	1. heart ⇨ bradycardia, ↓ contractility, ↓ conduction velocity in the AV node 2. vasculature ⇨ mediate vasodilation via synthesis of NO by endothelial cells 3. smooth muscle ⇨ ↑ tone in intestine & bladder; ↓ tone in sphincters 4. eye ⇨ contraction of sphincter (miosis) & ciliary muscle for near vision 5. exocrine glands ⇨↑ sweating (SNS), salivation & gastric acid secretion
	1. atropine - non-selective, long lasting 2. scopolamine – centrally acting 3. homatropine – shorter acting 4. pirenzepine - M1 receptor selective (anti-ulcer)	1. heart ⇨ tachycardia, ↑ AV node conduction 2. vasculature ⇨ no effect (no cholinergic innervation) 3. smooth muscle ⇨ relaxation in GI & urinary tract 4. eye ⇨ mydriasis & cycloplegia 5. exocrine glands ⇨ dry mouth, dry skin, & ↓ gastric acid secretion 6. CNS affects ⇨ belladonna toxicity (mad as a hatter, red as a beet, blind as a bat, hot as hell)

Acetylcholinesterase Inhibitors

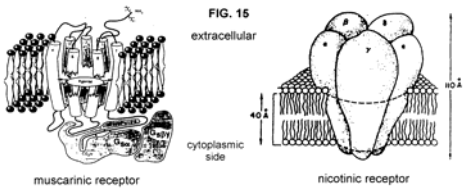
Rapidly reversible (competitive)	Edrophonium ⇨ used for myasthenia gravis (aka Tensilon)
Slowly reversible (competing substrate, carbamylates enzyme)	1. Neostigmine ⇨ does not cross BBB; affects skeletal muscle most strongly; used for myasthenia gravis & ileus 2. Physostigmine ⇨ crosses BBB, used for glaucoma and for treatment of belladonna poisoning 3. Pyridostigmine ⇨ used for myasthenia gravis 4. Ambenonium ⇨ used for myasthenia gravis 5. Demercarium ⇨ used for glaucoma
Irreversible or very slowly reversible (phosphorylates enzyme)	Organophosphate insecticides, nerve gases Echothiophate ⇨ used for glaucoma

Neurons of the ANS

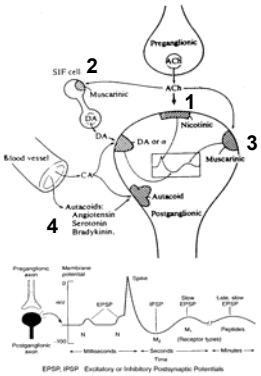


Structure and Physiology of the Autonomic Ganglion

- Ganglionic nicotinic (sympathetic & parasympathetic)
  - pentamer: 2 distinct subunits (α,ß) - α2ß3 or α3ß2
  - α chains contain the Ach binding sites
  - binding of Ach → opening of ion channel (Na+ in, K+out)



Structure of the Ganglia



1. N1 fast EPSP
2. M2 slow IPSP
3. M1 slow EPSP
4. Late, slow EPSP
   Autocoids, peptides

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

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

- **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

Site	Predominant ANS	Effect of Ganglionic Blockade

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*.