MYDRIATICS, CYCLOPLEGICS, AND MYDRIOLYTICS

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Overview

- Sympathetic NS
- Parasympathetic NS
- Mydriatics
  - Sympathomimetics
- Mydriatic-cycloplegics
  - Parasympatholytics
- Mydriolytics
Sympathetic NS – General Info
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[Diagram of sympathetic nervous system with labeled parts such as hypothalamus, ophthalmic division of trigeminal nerve, long ciliary nerve, to sweat glands of forehead, to smooth muscle of eyelid, to pupil, internal carotid artery, external carotid artery, third neuron, superior cervical ganglion, second neuron, Spinal cord, C2, T1. Focus on the first neuron.]
Sympathetic NS – General Info
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Diagram:
- CNS
- Superior Cervical Ganglion
- Adrenergic Division
- Acetylcholine
- Norepinephrine
- Effector Cell
Sympathetic NS – General Info

- **Neurotransmitters:**
  - **Pre-ganglionic** = acetylcholine
  - **Post-ganglionic** = norepinephrine (or epinephrine)

- **Termination of NE activity:**
  - Enzymatic inactivation
  - Diffusion
  - Reuptake at presynaptic NT
Sympathetic NS – General Info

- **Receptors:**
  - α and β
    - $\alpha_1$ on *post*-synaptic effector cell
    - $\alpha_2$ on *pre*-synaptic nerve terminal
    - β on *post*-synaptic effector cell
  - G-protein-linked

![Diagram of Sympathetic Nervous System](image)
• G-protein-linked receptors:
  • Binding of extracellular portion of receptor → altered interaction with cell membrane G-protein complex
  • $G_\beta - G_\gamma$ dissociates from GTP-$G_\alpha$
  • Both subunit portions interact with intracellular messenger pathways
Sympathetic NS – General Info

- **Receptors:**
  - $\alpha_1 \rightarrow$ phospholipase C activation $\rightarrow$ increased intracellular $\text{Ca}^{2+}$ $\rightarrow$ smooth muscle contraction
  - $\alpha_2 \rightarrow$ decreased NT release
  - $\alpha_2 \rightarrow$ inactivation of adenylate cyclase $\rightarrow$ decreased cAMP $\rightarrow$ inhibition of smooth muscle contraction
Sympathetic NS – General Info

• **Receptors**

  - $\beta_1$ and $\beta_2$ and $\beta_3$ → activation of adenylate cyclase → increase intracellular cAMP → various cAMP-mediated effects

  - $\beta_1$ primarily cardiac and
  - $\beta_2$ primarily vascular and smooth muscle of bronchi
Sympathetic NS – Ocular Innervation

- $\alpha_1$:
  - Iris dilator
  - CB
  - Orbital smooth muscle

- $\alpha_2$:
  - Iris sphincter
  - CB

- $\beta$:
  - Iris sphincter
  - CB
  - TM
Sympathetic NS Pharmacology

- **Sympathomimetics**
  - **Direct-acting = mimic NE**
    - Phenylephrine
    - Epinephrine
  - **Indirect-acting = increase NE availability**
    - Stimulate release of NE (hydroxyamphetamine)
    - Inhibit NE reuptake (cocaine)
Sympathomimetics in Ophthalmology

- **Uses:**
  - Diagnostic evaluation
  - Adjunctive surgical applications
  - (Glaucoma)
Phenylephrine

- Direct-acting $\alpha_1$-agonist

- 2.5% or 10% solution
  - Beyond 5%, higher concentration does not increase degree or duration of mydriasis
  - Lower efficacy in eyes with darkly pigmented irides
  - Efficacy increased with use of topical anesthetic

- Loses stability if exposed to light, heat, or air

Lam PTH, et al., Clin Experiment Ophthalmol 2003
Phenylephrine

• Side effects (list is not comprehensive!)
  • Discomfort upon instillation
  • Exfoliation of iridal pigment
  • Keratitis
  • Systemic hypertension, tachycardia, reflex bradycardia
  • Pulmonary edema

Pascoe PJ et al., JAVMA 1994
Phenylephrine

- **Contraindications**
  - Cardiac disease, hypertension, insulin-dependent diabetes, arteriosclerosis
  - Concurrent use in atropinized patients (tachycardia and hypertension)
  - Prolonged or sustained release routes not recommended
  - Only use 2.5% in infants and elderly patients
  - Only one drop of 10% per eye per hour

Epinephrine

• Direct-acting $\alpha$- and $\beta$- receptor agonist
• 0.5% to 2% solutions
• Poor intraocular penetration after topical administration
  • Dipivalyl epinephrine
• *May* augment mydriasis relative to $\alpha$-agonist monotherapy

• Intraoperative mydriasis and hemostasis
  • 1:10,000 (intracameral bolus)
  • 1:1,000,000 (irrigation fluids)
• Must be preservative- and bisulfate-free

Hydroxyamphetamine

- Indirect-acting adrenergic agonist
  - Increases NE release from post-ganglionic neuron
- Similar efficacy to phenylephrine
  - Not affected by iris color
  - Not affected by topical anesthetic
- Increased efficacy in combination
  - 1% solution with 0.25% tropicamide

- Uses:
  - Mydriatic in humans
  - Lesion localization in Horner’s

- Side effects:
  - Increase blood pressure
  - Tachyphylaxis
Cocaine

- Indirect-acting
  - Prevents reuptake of NE by post-ganglionic neuron
  - Anesthetic activity

- Uses:
  - (Mydriasis)
  - (Local anesthesia)
  - (Vasoconstriction)
  - Confirmation of Horner’s diagnosis

- Side effects:
  - CNS stimulation (systemic absorption is rapid with ocular administration)
  - Significant corneal epithelial damage

http://www.cvpharmacology.com/
Horner’s Syndrome

- Horner’s syndrome = unopposed parasympathetic tone
  - Miosis
  - Ptosis
  - Enophthalmos
  - Elevated third eyelid

- Cutaneous hyperthermia (especially in ruminants)
- Dry ipsilateral nostril (especially in ruminants)

- Decreased sweating (except in horses)
- Increased sweating (only in horses)
Horner’s Syndrome
Horner’s Syndrome

- First order (central) lesion = hypothalamus to T1-3
Horner’s Syndrome

- **First order (central) lesion** = hypothalamus to T1-3

- **Second order (preganglionic) lesion** = spinal cord to sympathetic trunk to cranial cervical ganglion
Horner’s Syndrome

- First order (central) lesion = hypothalamus to T1-3

- Second order (preganglionic) lesion = spinal cord to sympathetic trunk to cranial cervical ganglion

- Third order (postganglionic) lesion = cranial cervical ganglion to eye
## Efferent Sympathetic Lesion Localization

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Central</th>
<th>Pre</th>
<th>Post</th>
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</table>

**Diagram:**
- Central
- Pre-G
- Post-G
- EC
# Efferent Sympathetic Lesion Localization

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Degree of Dilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4% cocaine</td>
<td>Inhibits NE reuptake by post-ganglionic neuron</td>
<td>Central Impaired</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post None</td>
</tr>
</tbody>
</table>

**Central** ➔ **Pre-G** ➔ **Post-G** ➔ **EC**
## Efferent Sympathetic Lesion Localization

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<tbody>
<tr>
<td><em>4% cocaine</em></td>
<td>Inhibits NE reuptake by post-ganglionic neuron</td>
<td>Impaired</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><em>1% hydroxyamphetamine</em></td>
<td>Stimulates NE release by post-ganglionic neuron</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
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**MOA:**
- Inhibits NE reuptake by post-ganglionic neuron
- Stimulates NE release by post-ganglionic neuron
## Efferent Sympathetic Lesion Localization

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<tr>
<td>1% hydroxy-amphetamine</td>
<td>Stimulates NE release by post-ganglionic neuron</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
<tr>
<td>1% phenylephrine</td>
<td>Mimics NE at EFFECTOR CELL</td>
<td>Absent</td>
<td>Absent</td>
<td>Maximal</td>
</tr>
</tbody>
</table>
Parasympathetic NS – General Info
Parasympathetic NS – General Info

- **Neurotransmitters:**
  - Pre-ganglionic = acetylcholine
  - Post-ganglionic = acetylcholine
  - Termination of ACh activity:
    - Rapid
    - Acetylcholinesterase → choline + acetic acid
Parasympathetic NS – General Info

- **Receptors**
  - Nicotinic
    - Ion channel
    - Excitatory
Parasympathetic NS – General Info

- **Receptors**
  - **Muscarinic**
    - G-protein-linked
    - Subtypes M1 – M5
      - Location
      - Excitatory or inhibitory
      - Agonist/antagonist
Parasympathetic NS Pharmacology

- Parasympatholytics = anticholinergics
  - Antinicotinics = block ACh activity at nicotinic R
    - Curare and curare-like drugs
  - Antimuscarinics = competitively bind muscarinic R
    - Atropine
    - Tropicamide
    - Scopolamine
    - Cyclopentolate
Parasympatholytics – Details

- Variable specificity for subtypes among PS-lytics
  - Atropine, scopalamine are non-specific
  - Tropicamide more selective for M4

- Different species have different subtypes

- Part of explanation for variable response

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<thead>
<tr>
<th>Subtype</th>
<th>%</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
<td>M3</td>
<td>65 – 70%</td>
<td>Iris sphincter, CB</td>
</tr>
<tr>
<td>M2, M4</td>
<td>5 – 10%</td>
<td>Iris sphincter, CB</td>
</tr>
<tr>
<td>M1</td>
<td>7%</td>
<td>Iris sphincter, CP</td>
</tr>
<tr>
<td>M5</td>
<td>5%</td>
<td>Iris sphincter</td>
</tr>
</tbody>
</table>
Parasympatholytics in Ophthalmology

• Mydriasis – diagnostic and therapeutic

• Cycloplegia –
  • Treat myopia: relaxation of CB relaxes accommodation, reduces tension that leads to elongation of eye and resultant myopia
  • Treat amblyopia: visual blur in good eye forces ‘lazy’ eye to pick up the slack
  • Refraction: cycloplegia allows assessment of true refraction
  • Treat uveitis
Atropine

- Nonselective muscarinic antagonist
- Comparatively poor penetration
- Stability is pH- and temperature-dependent
- Most potent cycloplegic available
- Iridal binding leads to depot
- Rapid onset, prolonged duration

- Predominantly used for treatment of uveitis

- May be used for refraction or correction of amblyopia or myopia

*Atropa belladonna* (Deadly nightshade)
Atropine

- **Side effects**
  - Local irritation

- Increase IOP
  - Angle-closure glaucoma
  - Open-angle glaucoma (unpredictable)

- Rapid systemic uptake:
  - Systemic peripheral effects predominate over central effects
  - Decreased salivation, facial flushing, decreased sweating, urinary retention, excitement,…
  - Worse in young and elderly patients (convulsions)
Atropine in animals

- **Dogs:**
  - Systemic $\rightarrow$ increase IOP; mydriasis
  - Topical $\rightarrow$ increase IOP; increase HR

- **Cats:**
  - Topical $\rightarrow$ increase IOP

- **Horses:**
  - Topical $\rightarrow$ increase IOP; decrease IOP; altered GI motility
  - Subconjunctival $\rightarrow$ altered GI motility

Kovalcuka L, et al., VO 2015
Greenberg S, et al., VO 2015
Stadtdaumer K, et al., VO 2006
Herring I, et al., VO 2000
Mughannam AJ, et al., VO 1999
Williams MM, et al., VO 2000
Homatropine

- Nonselective muscarinic antagonist
  - Partially synthetic, partially naturally-derived
  - 1/10 potency of atropine
  - pKa 9.9 → primarily ionized at physiologic pH → poorly diffusible

- Relatively weak but prolonged mydriatic and cycloplegic effect

**Uses:**
- Treatment of anterior uveitis

**Side effects:**
- As for atropine
Scopolamine (hyoscine)

- Nonselective muscarinic antagonist
- Comparable to atropine
  - Highly potent
  - Shorter duration of action
- Positive chronotropic effects
- Greater incidence of idiosyncratic reactions

**Uses:**
- Cycloplegic refraction
- Anterior uveitis

**Side effects:**
- CNS toxicity (acute psychosis)

*Hyoscyamus niger* (henbane)
Cyclopentolate

- Nonselective muscarinic antagonist
- pKa 8.4 → primarily ionized at physiologic pH → poorly diffusable
- Effects greatly influenced by iridal pigmentation
- Effects comparable to atropine but shorter

**Uses:**
- Cycloplegic refraction (agent of choice in most)
- Anterior uveitis
- Intraoperative mydriasis

**Side effects:**
- Irritation
- Corneal epithelial toxicity
- IOP elevation
- Greater CNS effects than atropine
  - Drowsiness, ataxia, slurred speech
  - Worse in young, neurologically impaired
Tropicamide

- Nonselective muscarinic antagonist, possibly more selective for M4
- pKa 5.27 → 2.3% ionized at physiologic pH → best intraocular penetration of mydriatic-cycloplegics

- Rapid onset, short duration
  - Cycloplegic action is concentration-dependent (mydriatic effect is not)
  - Mydriatic effects less influenced by iris pigmentation
  - Duration prolonged by prior application of topical anesthetic

- Combination with hydroxyamphetamine ideal in humans for mydriasis with minimal effect on accommodation

- **Side effects:**
  - Discomfort
  - IOP increase
  - Low risk for systemic side effects because even though absorbed, low affinity for systemic M receptors
Tropicamide in animals

• **Dogs:**
  • Increase IOP

• **Cats:**
  • Increase IOP (in treated and untreated eye)
  • Decrease STT

• **Horses:**
  • Decrease STT
  • No impact on streak retinoscopy

Taylor N, et al., VO 2007
Wallin-Hakanson, N, et al. VO 2001
Margadant D, et al., VO 2003
Stadtbaumer K, et al., VO 2006
Stadtbaumer K, et al., VO 2002
Gomes F, et al., VO 2011
Ghaffari M, et al., VO 2009
McMullen RJ, et al., VO 2014
Mydriolytics
Mydriolytics

- Goal = safe and effective reversal of mydriatics

- Option = cholinergic agonist (i.e., pilocarpine) to reverse adrenergic agonist (i.e., phenylephrine)
  - Drawback = cholinergic agonist increases risk of accommodative CB spasm, angle-closure glaucoma, and pupillary block
  - Drawback = stimulation of dilator and constrictor simultaneously leads to shallow AC and risk of pupillary block (in humans)
Dapiprazole

- Reverses mydriasis by blocking iris dilator $\alpha_1$- receptors

- Produces miosis and decreases IOP
  - Concentration-dependent miosis within 10 min, duration up to 6 hours
  - More rapid in eyes with lighter-colored irises
  - IOP reduced up to 6 hours

- Partially reverses cycloplegia

- **Use:**
  - Reversal of phenylephrine-, homatropine-, or tropicamide-induced mydriasis
  - 2 drops, then 2 drops 5 minutes later, although 1 drop may be sufficient
Summary

- **Sympathomimetic mydriatics:**
  - Phenylephrine, epinephrine (direct-acting)
  - Hydroxyamphetamine, cocaine (indirect-acting)

- **Parasympatholytic mydriatic-cycloplegics:**
  - Atropine
  - Homatropine
  - Scopolamine
  - Cyclopentolate
  - Tropicamide

- **Mydriolytic:**
  - Dapiprazole
Questions?