Comparative Neuro-Ophthalmology

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Suggested Reading


Neuroophthalmology

I. The Pupil
II. Visual Pathways
III. Ocular Movement
IV. Eyelid and Nictitans Movement
V. Lacrimation
Anatomic Pathways: Afferent Arm of PLR

- Retina
- Optic nerve
- Optic chiasm
- Optic tract
- Pretectal nuclei
- CNIII parasymathetic nuclei
AFFERENT ARM OF PLR: RETINA:

- rod/cone photoreceptors
- retinal bipolar cells
- retinal ganglion cells and axons

- intrinsically photosensitive RGCs*
Afferent Arm of PLR: Optic Chiasm

- optic nerve fibers converge at chiasm
- species dependent differential decussation (crossing-over) of fibers correlating with frontal position of eyes:
  - primate 50%
  - feline 65%
  - canine 75%
  - equine, bovine, porcine 80-90%
  - rodents 97%
  - most submammals 100%*
Afferent Arm of PLR: Optic Tract

- Post-chiasmal fibers:
  - ~80% of fibers synapse in *dorsal lateral geniculate body (LGB)* (thalamus) = visual fibers
  - ~20% of fibers bypass LGB:
    - Many synapse in *pretectal nuclei (PTN)*
Intrinsically Photosensitive Retinal Ganglion Cells (ipRGC)


- Subset of RCG (2%) that are photosensitive (melanopsin)
- Project to brain centers that control non-visual functions including circadian related behavior (hypothalamus) and PLR (pretectal nuclei)
- RGCs regulate acute changes in pupil size; ipRGC control sustained pupil size in response to environmental light levels
- In normal retina, input to ipRGC predominately from rod/cones
- ipRGC capable of generating PLR (and reportedly dazzle reflex) without rod/cone input, requires high intensity light in ~480nm wavelengths (blue)
20% Optic Tract Fibers Bypassing Lateral Geniculate Body

- Synapse in hypothalamus (base of diencephalon) to regulate circadian rhythm
- Synapse in pretectal nuclei (at junction of diencephalon and tectum) to elicit PLR
- Synapse in rostral colliculi (tectum):
  - dazzle reflex
  - redirection of gaze and movement of head and neck in response to visual stimuli
- Synapse in rostral colliculi to project to the reticular activating system
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Afferent Arm of PLR: Pretectal Nuclear Fibers

- at caudal commissure, some fibers stay ipsilateral, others cross over to contralateral CNIII nuclei, (*second decussation proportional to first at chiasm*):
  - Unilateral afferent stimuli results in bilateral efferent effect…. basis for consensual PLR
  - Humans:
    - 50% decussation at each juncture
    - *direct PLR = indirect PLR*
    - *no anisocoria in ambient light with afferent arm defect*
  - Sub-primate mammals:
    - >50% decussation at each juncture
    - “*dynamic contraction anisocoria*”
    - *direct PLR > indirect PLR*
    - *anisocoria with unilateral afferent arm defect*
  - Most submammals:
    - 100% decussation
    - *no indirect PLR*
Efferent PLR Pathway

- Pupillomotor (preganglionic) fibers originate parasympathetic nuclei of CN III (Edinger-Westphal nucleus), join with motor fibers of CN III
- CNIII courses ventrally through midbrain, through cavernous sinus and out orbital fissure, diverge from motor fibers off ventral ramus of CNIII in orbital cone near ciliary ganglion

Figure III-1 Overview of the oculomotor nerve.

From Cranial Nerves 3rd Ed. ©2010 Wilson-Pauwels, Stewart, Akesson, Spacey, PMPH-USA
Postganglionic Efferent

- Synapse in ciliary ganglion
- Short ciliary nerves
  - Dog = 5-8 short ciliary nerves….mixed fibers with parasympathetic, sensory afferent from CNV (nasociliary nerve)
  - Cat = 2 short ciliary nerves (malar and nasal), only parasympathetic
Postganglionic, Parasympathetic Cat

Ciliary Ganglion

Nasal N.

Malar N.

medial

lateral
Iris Musculature Neurophysiology

- Mammals:
  - Smooth muscle
  - Sphincter mm = cholinergic (parasympathetic), through short ciliary nerves; *acetylcholine*
  - Dilator mm. = adrenergic (sympathetic), through long ciliary nerves; *norepinephrine*
  - *Reciprocal innervation with inhibition of antagonist iris mm.*

- Most sub-mammals:
  - Skeletal muscle
  - Degree of voluntary control of pupillary movement
  - Parasympatholytic mydriatics not effective
Ciliary Body Innervation and Accommodation

- Efferent parasympathetic through CNIII, short ciliary nerves
- Efferent sympathetic through long ciliary nerves (disaccomodation)
- Longitudinal, radial, circular ciliary body mm.

- Primates=cholinergic stimulation ⇒ ciliary mm. contraction ⇒ relaxation of zonules ⇒ increased axial distance/curvature (disaccomodation occurs through adrenergic stimulation)

- Carnivores (cat, raccoon, ground squirrel)=accommodation through anterior change in lens position within eye (“translation” accommodation”, preponderance of longitudinal mm. in subprimate mammals)
Other Pupillary Reflexes: Accommodation Reflex

- “Accommodation-convergence reflex” or “near reflex”
- Afferent = CNII
- Efferent = CNIII (also inhibition of CN VI)

- Stimuli = focusing on near object
- Effect =
  - accommodation (change in lens shape)
  - constriction of pupil (increase depth of focus)
  - medial convergence of eyes (medial rectus with inhibition of lateral rectus)

Video
Other Pupillary Reflexes: Ciliospinal Reflex (Pupillary-Skin Reflex)

- Afferent = CNV
- Efferent = oculosympathetic pathway
- 1-2 mm dilation of the ipsilateral pupil in response to pain applied to the ipsilateral neck, face, and upper trunk
- Absent in Horner’s syndrome

Video
Axon “Reflex”

- “Sensory activity ascends a branch of nerve until bifurcation, then retrograde transmission, causing a neuroeffector response without passing through the brain stem or spinal cord”
  - Prodromic axoplasmic flow/transmission
  - Antidromic axoplasmic flow/transmission
Axon “Reflex” - Reflex Uveitis

- stimulation of ophthalmic division of CN V (cornea, conjunctiva, eyelids)
  - prodromic transmission until bifurcation at iris/ciliary body
  - antidromic transmission to iris/ciliary body
- Effect = release of prostaglandins, substance P, vasoactive compounds, other inflammatory mediators, AcH
- Outcome = miosis, ciliary body spasm, disruption of blood-aqueous barrier, ocular hypertension in some species

Other Factors Modifying the Pupil and PLR

- PLRs present at opening of eyelids, but may be sluggish until maturation of retina (28 days dog)

- active = direct adrenergic input from psychosensory stimulation (fear)

- passive = supranuclear inhibition of parasympathetic fibers of CN III
  - descending, inhibitory pathways from cortex to CNIII parasympathetic nuclei
  - this inhibition lost with sleep, anesthesia, opiodes, extensive cerebral cortical lesion….resulting in miosis
Evaluating Pupillary Light Reflexes

- Evaluate resting pupil size in room and dim light

- Evaluate direct and indirect or consensual PLR (indirect = PLR to fellow eye...denote as "consensual response from OD to OS" or ".....OS to OD"):
  - in sub-primate mammals, direct PLR > indirect PLR
  - in most submammals, no consensual PLR due to complete decussation at chiasm
  - note pseudo-indirect PLR in birds resulting from scatter illumination from illuminated eye to non-illuminated eye eliciting a direct PLR

- Swinging Flashlight Test and Cover/Uncover Test

- Chromatic PLR testing (ipRGCs)

- Dark adaptation testing
Swinging Flashlight Test

- Light alternately shifted from one pupil to other, with 2-3 seconds of direct stimulation in each eye
- Normal...both pupils constrict to equal degree when stimulated, illuminated eye produces slightly more constriction
Swinging Flashlight Test

- “Positive” test (Marcus-Gunn pupil)…illuminated eye dilates:
  - “Relative Afferent Pupillary Defect” (RAPD)
  - unilateral prechiasmal lesion (optic nerve or retina) in humans
  - can be associated with either pre- and post-chiasmal afferent arm lesions in sub-primate mammals

- “Pupillary escape” (dilate slightly after initial contraction):
  - can be normal (adaptation of stimulated retina)
  - may result from incomplete unilateral, afferent arm lesion, results from scatter illumination entering (fellow) normal eye, causing an initial indirect PLR

Therefore, “positive” test followed by “cover-uncover” test…(cover each eye with hand and ambient light is stimuli) to eliminate influence of scatter illumination
Evaluation of Retinal Status Using Chromatic Pupil Light Reflex Activity in Healthy and Diseased Canine Eyes

Sinisa D. Grozdanic,1 Milan Matic,1 Donald S. Sakaguchi,2 and Randy H. Kardon3

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Slide Courtesy of Dr. Andras Komaromy
Chromatic Testing of PLR

- **Normal:**
  - Positive red light
  - Positive blue light

- **Photoreceptor disease (SARDS, PRA, acute retinal detachment):**
  - Negative red light
  - Positive blue light

- **Retinal ganglion cell disease (optic neuritis, ON neoplasia, ON hypoplasia, ON avulsion):**
  - Negative red light
  - Negative blue light

*White light contains all wavelengths in visible spectrum incl. blue…*positive PLR with bright white light does not rule out photoreceptor disease*
Dark Adaptation Test

- Assessment of pupillary size after 5 minutes in dark
- Examine with direct ophthalmoscope at an arm’s distance, turned on immediately prior to assessment so as not to stimulate PLR
Dark Adaptation Test

- normal = both pupils dilate fully and symmetrically
- afferent and efferent lesions = both pupils dilate
- mechanical restriction problems (e.g. synechiae) = affected pupil fails to dilate
- sympathetic denervation = affected pupil fails to dilate, anisocoria accentuated by dark adaptation
**General Principles of Lesion Localization**

**Afferent Lesion (before LGB)**: vision AND PLR AND dazzle reflex abnormal

**Efferent Lesions**: PLR abnormal, vision and dazzle reflex normal

**Cortical Lesion**: Vision abnormal, PLR and dazzle reflex normal

*objective assessment of vision and PLR
*partial lesions
*ipRCGs
Unilateral Retinal Chain, Intraocular Retinal Ganglion Cell Lesions

- anisocoria in ambient light with larger pupil ipsilateral to lesion (subprimate mammals)
- deficit of direct and consensual PLR in affected eye
- positive swinging flashlight test and cover-uncover test
- normal dark adaptation test

- visual deficits

*PLRs and dazzle reflex may persist with advanced (outer) retinal disease with visual deficits (ipRCGs)
Unilateral Prechiasmal Optic Nerve Lesions

- signs identical to retinal disorders
Unilateral Optic Tract Lesions (Anterior to Lateral Geniculate Body)

- similar to unilateral prechiasmal lesion but dilated pupil contralateral to lesion
- more subtle anisocoria v. prechiasmal lesion
- positive swinging flashlight test contralateral to lesion (*see notes for proof, B. Blacklock)
- more miotic pupil persists in the same eye (ipsilateral to lesion) regardless of which eye is stimulated

- visual field contralateral to affected tract is diminished or lost
  - contralateral homonymous hemianopia (vision loss most obvious in eye contralateral to lesion)
Bilateral Retina, Optic Nerve or Tract, Optic Chiasm or Caudal Commissure Lesions

- bilateral mydriasis, PLR deficits, visual deficits commiserate with severity of lesion

- lesions in both retinas more common than (> chiasm > bilateral optic nerves > bilateral caudal commissure > bilateral optic tracts
Efferent Arm Lesions

- Ipsilateral dilated pupil, anisocoria often more pronounced than afferent arm lesion
- Nonreactive (ipsilateral) pupil to direct and indirect light,...i.e. negative direct PLR, negative consensual PLR from normal eye to affected eye (side)
- Normal dark adaptation test
- Normal optic dazzle reflex and menace response
Efferent Arm Lesions

- Preganglionic (ciliary ganglion):
  - in non-humans, almost always CNIII motor and pupillomotor (total ophthalmoplegia)

- Postganglionic:
  - pupillomotor fibers only (internal ophthalmoplegia) as motor fibers diverge from pupillomotor fibers in orbit shortly before ciliary ganglion
  - hemipupil in cats if affecting only one short ciliary nerve
  - supersensitivity to parasympathomimetics
Internal Ophthalmoplegia

- “Impairment of pupillary function (sphincter m, atropine, parasympathetic innervation)
- Parasympathetic efferent denervation (pupillomotor fibers), ocular movement (motor fibers) unaffected
- Almost always post-ganglionic, often idiopathic and self-resolving (analogous to “Adie Tonic Pupil” in humans)
- D or Reverse D shaped pupil in cats if only one short ciliary artery affected
- Pupillomotor fibers superficial (medial) and smaller in diameter in CNIII
  - In humans, may be preferentially affected with compressive lesions (e.g. aneurism)
  - In humans, preferentially spared with microvascular diseases (e.g. diabetes, hypertension)
External Ophthalmoplegia

- motor denervation of CNIII
- In dogs/cats, isolated external ophthalmoplegia (without pupillomotor signs) is rare, associated with discrete central lesions affecting (motor) nucleus of CNIII
Total Ophthalmoplegia

- internal and external ophthalmoplegia
- by definition, a preganglionic lesion (re: ciliary ganglion),
  - generally, intracranial lesion, as pupillomotor and motor fibers of the ventral ramus of CNIII diverge about mid-orbit
  - i.e. intraorbital cause of total ophthalmoplegia uncommon and caused by lesion in caudal orbit
Pharmacologic Localization of Lesions of Autonomic Innervation to Eye

- Direct testing stimulates receptor
- Indirect testing affects release or reuptake of neurotransmitter
Limitations/Caveats in Pharmacologic Testing for Autonomic Disorders

- requires normal, control eye
- quantity of absorbed drug affected by volume, corneal epithelium, etc.
- prior drug action (wait 24 hours minimum)

- acute lesion, denervation hypersensitivity may not have yet developed
- partial lesions, partial denervation hypersensitivity
- pre-ganglionic lesion, partial denervation hypersensitivity
Pharmacologic Testing with Parasympathetic Denervation

- Denervation hypersensitivity > with ganglionic or postganglionic lesions

- 0.5% physostigmine (indirect parasympathomimetic, allows buildup of acetylcholine at synaptic fissure):
  - Postganglionic = no constriction (no AcH at synaptic fissure)
  - Preganglionic = constriction before normal, control eye (basal release of AcH occurs, partial denervation hypersensitivity)
Pharmacologic Testing with Parasympathetic Denervation

- 2% pilocarpine (direct parasympathomimetic):
  - 24 hours post indirect agent testing
  - postganglionic lesion constricts sooner than normal eye
  - preganglionic lesion constricts similar timeframe to normal eye**

- some clinicians use 0.05% pilocarpine, no effect on normal eye

- failure to respond to both tests indicates pharmacologic blockade or iridal disease (atrophy, synechia)
Oculosympathetic Pathway

- sympathetic efferent:
  - central
  - preganglionic
  - postganglionic
Efferent Sympathetic Pathway: 1st Order Neurons

- sympathetic fibers arise from hypothalamus
- lateral tectotegmentospinal tract
- descend ipsilaterally through brain stem and lateral funiculus of spinal cord
- synapse in preganglionic cell bodies in gray matter of intermediolateral column of spinal cord T1-T4
Efferent Sympathetic Pathway: 2nd Order Neurons

- rami communicans through ventral roots
- thoracic sympathetic trunk
- cervicothoracic and middle cervical ganglia, cervical sympathetic trunk
- synapse in cranial cervical ganglion (caudomedial to tympanic bullae) with postganglionic sympathetic neurons
Efferent Sympathetic Pathway: 3rd Order Neurons

- postganglionic fibers join tympanic branch of CN IX (glossopharyngeal n.) to form caroticotympanic nerves
- over promontory of middle ear
- exit middle ear and enter cavernous sinus
- join CN V
- most fibers pass through ophthalmic division of CNV, to nasociliary nerve (to levator mm., smooth mm. of orbit) and then continue into globe via the long ciliary neve in the suprachoroidal space to iris dilator m.
- some fibers through maxillary division of CNV to infraorbital/zygomatic nerve to supply lower eyelid and nictitans
Efferent Sympathetic Pathway: 3rd Order Neurons
Horner Syndrome

- protrusion of nictitans
- ptosis
- miosis
- enophthalmos

- cutaneous facial and cervical hyperthermia and decreased sweating (peripheral vasodilatation)
Efferent Sympathetic: Horner Syndrome

- cutaneous facial and cervical hyperthermia and conjunctival hyperemia (peripheral vasodilation)
- anisocoria (dark adaptation, and excitement accentuate)
- ptosis and "reverse ptosis"
- enophthalmos variably present......narrowed palpebral fissure (ptosis and reverse ptosis) creates impression of "apparent" enophthalmos even if not present
Horner Syndrome in Large Animals

- signs more subtle than dogs/cats
- ptosis most consistent finding, miosis inconsistent
- ipsilateral cutaneous facial and cervical hyperthermia

- cattle = ipsilateral lack of sweating (anhydrosis, detected in nose), vascular engorgement of pinna (sweating mediated by alpha adrenergic receptors)

- horse = ipsilateral facial sweating (vasodilatation and increased blood flow from decreased vasomotor tonus)
  - entire ipsilateral head and body = first order lesion
  - ipsilateral head and neck = second or third order lesion
Pourfour du Petit Syndrome

- Mydriasis, widened palpebral fissure, exophthalmos (opposite of Horner)
- Oculosympathetic hyperactivity (irritative lesion)
- Reported in 3 cats following ear flushing
Pharmacologic Testing for Horner Syndrome

- 6% cocaine...blocks reuptake of norepinephrine
  - no mydriasis confirms Horner’s syndrome
- 1% hydroxyamphetamine...causes norepinephrine release
  - postganglionic = no or incomplete mydriasis
  - preganglionic = normal mydriasis
- 10% phenylephrine
  - hypersensitivity with postganglionic
  - mydriasis in 5-8 minutes
  - retraction of nictitans and resolution of ptosis also occurs
  - some clinicians use 1% phenylephrine
Apraclonidine (0.5-1%) Testing

- Used in lieu of cocaine to establish diagnosis of Horner syndrome in humans
- Strong alpha 2 agonist, weak alpha 1 agonist, produces slight miosis in normal human eye
- Denervation hypersensitivity causes proliferation of alpha-1 receptors in the dilator muscle
- The denervated pupil dilates, slight miosis in normal eye
- Reportedly does not distinguish pre vs. post ganglionic lesion

- Apraclonidine induces moderate mydriasis (30%) in normal dogs, moderate miosis in normal cats
Localization of Pupillary Abnormalities

- First rule out non-neurologic conditions:
  - psychosensory stimulation
  - axon reflex or anterior uveitis
  - mechanical iris lesion (e.g. glaucoma, lens luxation)
  - structural iris lesion (e.g. synechia or iris atrophy)
  - pharmacologic blockade

- If neurologic disorder, define effects on:
  - pupillary diameter or shape
  - pupillary light reflex using swinging flashlight test
  - response to dark adaptation testing

- Concurrently evaluate:
  - menace response and dazzle reflex (localizing for afferent arm lesion)
  - ocular position and motility (motor deficit CNIII, using vestibulo-ocular reflex and redirection of gaze)
  - funduscopic exam
  - complete cranial nerve and neurologic exam
Special Notes on Pupil Size and PLR and Intracranial Lesions

- **Cerebellar** lesions may cause unilateral (contralateral) or bilateral mydriasis with normal PLR
- Acute cerebral or brainstem swelling may cause ipsilateral or bilateral mydriasis/PLR deficit from compression of CNIII
- Extensive cerebro-cortical lesion may be associated with bilateral miosis (loss of supranuclear inhibition of CNIII)
- Experimental rostral colliculi lesions in dogs associated with bilateral miosis
Feline Spastic Pupil Syndrome

- Inconsistent or alternating anisocoria which persist with dark adaptation
- FeLV neuritis of sympathetic, parasympathetic or both
- Risk factor for development of lymphoproliferative disease
Feline Dysautonomia (Key-Gaskell Syndrome)

- Idiopathic, diffuse polyneuropathy of autonomic nervous system (r/o toxic or environmental)
- Mydriatic, unresponsive pupils
- Anisocoria
- Prolapsed nictitans
- Decreased tear production
Questions?
Index: Summary of Localization of Pupillary Abnormalities

- Anisocoria
  - unilateral mydriasis
  - unilateral miosis
- Bilateral mydriasis
- Bilateral miosis

Anisocoria: Unilateral Mydriasis

- Efferent arm lesions:
  - more obvious anisocoria than afferent arm lesion
  - absent direct PLR, normal indirect PLR from affected eye to fellow eye
  - concurrent external ophthalmoplegia if intracranial lesion
  - may have “D” and “reverse D” in cat if postganglionic
  - supersensitivity to parasympathomimetics esp. if postganglionic
Anisocoria: Unilateral Mydriasis

- Afferent arm lesions:
  - less obvious anisocoria (from bilateral afferent input)
  - absent direct PLR and indirect PLR from affected eye/side to fellow eye if prechiasmal
  - more mydriatic pupil and PLR deficit contralateral to lesion if postchiasmal (optic tract)
  - positive swinging flashlight test with pre and post chiasmal lesion in dogs/cats (only with prechiasmal lesion in humans)
  - menace response and dazzle reflex deficits
Anisocoria: Unilateral Mydriasis

- Cerebellar lesions
  - generally contralateral mydriasis +/- ipsilateral nictitans protrusion
  - both pupils respond to light stimuli

- Acute cerebral swelling
  - ipsilateral mydriasis from compression of CN III
Anisocoria: Unilateral Miosis

- Efferent sympathetic
  - ipsilateral miosis
  - anisocoria accentuated by dark adaptation
  - further constriction on light stimulation
  - other clinical findings of Horner’s syndrome
  - pharmacologic localization
Localizing Horner’s Syndrome with Other Neurologic Signs

- Cervical spinal cord = tetraparesis
- C6-T2 spinal segments = forelimb monoparesis with reduced spinal reflexes
- Cervical sympathetic trunk = no other deficits
- Inner/middle ear = possible CN V, VI, VII, VIII, IX deficits
- Cavernous sinus = possible CN III, IV, V, VI deficits
- Retrobulbar space = concurrent parasympathetic denervation, possible CN II, III, IV, V, VI deficits
Bilateral Mydriasis

- Bilateral afferent
  - retinal disease more common than (> optic chiasm > bilateral optic nerve > bilateral optic tract
  - concurrent menace/dazzle deficits

- Bilateral efferent
  - bilateral CNIII rare
  - e.g. brainstem lesions affecting parasym pathetic nucleus of CNIII
Bilateral Miosis

- Loss of supranuclear inhibition of CNIII
  - Sleep, opioids, general anesthesia
  - Extensive cerebral cortical lesion
- Experimentally, reported with rostral collicular lesions in dogs