Anisocoria: small versus large pupils

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LAURENT GAROSI explains how pupils are a vital window into the neurologic status of animals' nervous systems

THE pupil is an important indicator of the neurologic health of the central and peripheral nervous systems.

Through the sympathetic and parasympathetic nerve pathways that innervate the iris, the pupil regulates the amount of light that reaches the retina.

The pupil size is in a constant state of flux – a result of labile, dynamic equilibrium between the sympathetic and parasympathetic innervations. Animals with pupils of unequal size (anisocoria) or shape (dyscoria) must be found free of primary or secondary anatomic or mechanical abnormalities before consideration is given to a neurologic dysfunction. Examples of primary or secondary anatomic or mechanical disorders include iris atrophy, uveitis, glaucoma, subluxated lenses and synechia.

Parasympathetic innervation

The ocular parasympathetic tract is a two-neuron pathway mediated by the parasympathetic component of the oculomotor nerve – cranial nerve III (CNIII) – see Figure 1. It is involved in the control of pupillary constriction, while the oculomotor nerve is responsible for the motor innervation of the levator palpebrae superioris (elevation of the upper eyelid) and ipsilateral dorsal, ventral and medial recti extraocular muscles, as well as the ventral oblique muscle (movement of the eyeball).

Parasympathetic denervation of the pupil – internal ophthalmoplegia (Figure 2) – can occur with or without disturbing the motor innervation of the oculomotor nerve (external ophthalmoplegia).

Clinical signs of internal ophthalmoplegia include a widely dilated pupil that is non-reactive to direct and indirect light stimulation. The anisocoria is particularly obvious in ambient light, while maximal and equal dilation of both eyes occurs on dark adaptation.

External ophthalmoplegia is characterised clinically by ptosis of the upper eyelid, lateral strabismus (with an inability to move the globe dorsally, ventrally or medially) and signs of internal ophthalmoplegia.

Common causes of internal ophthalmoplegia include pharmacologic blockade with atropine or an atropine-like compound, cavernous sinus syndrome, mesencephalic lesion and orbital diseases.

Sympathetic innervation

The ocular sympathetic tract is a three-neuron pathway (Figure 3). The central or upper motor neuron pathway begins in the hypothalamus and descends in the spinal cord through the lateral tectotegmentospinal tract, to synapse on the lower motor neuron (LMN).

The LMN is divided in the preganglionic and postganglionic neurons. The preganglionic axons leave the spinal nerve in the segmental ramus communicans, which joins the thoracic sympathetic trunk inside the thorax ventrolaterally to the vertebral column.

It then continues cranially along the cervical sympathetic trunk, where it is part of the vagosympathetic trunk within the carotid sheath, and synapses with the bodies of the postganglionic cells in the cranial cervical ganglion that lies deep to the tympanic bulla.

Postganglionic axons enter the middle ear and the middle cranial fossa, where they join the ophthalmic branch of the trigeminal nerve running to the orbit.

The sympathetic nervous system innervates and provides tone to the smooth muscle of the eye and eyelids. This tone keeps the eyeball protruded and the eyelids and third eyelid retracted, causing the palpebral fissure to widen and the third eyelid to be pulled ventrally.

The tone of the iris dilator muscle is also maintained by the sympathetic system, which keeps the pupil partially dilated under normal conditions and dilates it during periods of darkness, stress, fear and painful stimuli.

Sympathetic denervation of the eye results in Horner’s syndrome. Clinical signs include myosis, drooping of the upper eyelid (ptosis), enophthalmia, and protrusion of the third eyelid (Figure 4).

Damage anywhere along the sympathetic pathway can cause Horner’s syndrome. This syndrome is particularly observed with lesions affecting the postganglionic fibres (otitis media, middle ear neoplasm, orbital disease, idiopathic) or preganglionic fibres (brachial plexus tumour or injury, cranial mediastinal mass and neck injury).

Horner’s syndrome is usually classified according to the level of the lesion along the sympathetic pathway as first order, second order (preganglionic) or third order (postganglionic).

Evaluation methods

A clinical approach to anisocoria involves the following steps:

• ophthalmologic examination to rule out non-neurologic causes (primary or secondary anatomic or mechanical pupil abnormalities);

• determining which pupil is abnormal by checking the pupillary light reflex and finding out if the asymmetry in pupil size increases in bright light or in darkness; and

• determining if the lesion is preganglionic or postganglionic by pharmacological testing and looking for other neurological signs.

• Pupil size and symmetry

Assessment of pupillary size and equality should be determined in ambient light, as well as in darkness. Normally, the pupil of each eye should be symmetrically shaped and equal to each other in size (Figure 5).

• Pupillary light reflex

Like any other reflex, the pupillary light reflex (PLR) involves an afferent arm and an efferent arm. The afferent arc of this reflex shares some common pathways (up to the level of the optic tract) with part of the afferent arc of the menace response.

The first neuron in this arc is the bipolar cell of the retina. This receives impulses from the neuroepithelial cells of the retina (rods and cones).

The second afferent neurone is the ganglion cells of the retina. Its axons lie in the optic nerve and continue through the optic chiasm and proximal part of the optic tract of the opposite side (65 per cent decussation in cats and 75 per cent decussation in dogs).

While axons involved with vision reach conscious level after synapsing with the lateral geniculate nucleus, the axons involved in the PLR synapse with a third neuron in the pretectal nucleus. Most

of the axons arising from this nucleus decussate again and synapse with the oculomotor nucleus (parasympathetic component) ipsilateral to the stimulated eye. There are also neurons that do not decussate and which project to the oculomotor nucleus on the contralateral side of the stimulated eye. The proportion of axons that decussate is higher than the one that does not decussate. This explains why the direct response (constriction in the eye receiving the light stimulus) is greater than the consensual response (constriction in the eye not receiving the light stimulus).

The efferent arm of this reflex is a two-neuron pathway mediated by the parasympathetic portion of the third cranial nerve (oculomotor nerve or CNIII). The preganglionic neuron enters the orbit through the orbital fissure and synapses with the postganglionic neurone's cell body in the ciliary ganglion.

The axons of this second neurone innervate the iris and ciliary body musculature (Figure 6).

• Dark adaptation test

The eyes should be allowed to dark-adapt in complete darkness for a couple of minutes. Both pupils will dilate maximally and equally. A direct ophthalmoscope can be used as a pupillometer, but without the light source turned on until immediately prior to assessing the pupil.

The efferent sympathetic pathway that controls the iris dilator muscles comprises a chain of three neurones:

– the upper motor neurone (the cell bodies of which lie in the hypothalamus) sends axons through the brainstem and cervical spinal cord to form the tectotegmentospinal pathway and synapses with preganglionic neuronal cell bodies;

– the preganglionic neurone (the cell bodies of which are located in the grey matter of the T1-T3 spinal cord segment) sends axons that leave the spinal cord via the segmental ventral roots to the paravertebral sympathetic chain, then extends rostrally along the thoracic and then the cervical vagosympathetic trunk before synapsing in the cranial cervical ganglion; and

– the postganglionic neurone (the cell bodies of which are located in the cranial cervical ganglion) sends axons that cross the middle ear, enter the cavernous sinus and enter the globe via the long ciliary nerve.

• Swinging flashlight test

This test assesses the integrity of the entire pupillary light reflex pathway. It is best conducted in a darkened room, as the extent of the iris constriction will be greater and more easily observed.

A strong light is alternatively swung from one eye to the other. If the pupil dilates during direct light

stimulation (instead of the expected pupil constriction), the swinging flashlight test is said to be positive for the eye with the dilating pupil (the direct stimulus is no longer sufficient to maintain the previously evoked degree of pupillary constriction, so both pupils dilate while maintaining the relative anisocoria).

A positive swinging flashlight test indicates an unilateral prechiasmal optic nerve disease and/or unilateral retinal disease.

• Pharmacologic localisation

These pharmacologic tests should be conducted on both eyes, using the normal eye as a control comparison.

– **Sympathetic denervation**

Along with other neurological abnormalities, pharmacological testing can be used to localise the site of the lesion. Administer 10 per cent phenylephrine[1] (a direct-acting sympathomimetic drug) topically to both eyes and note the time taken for the pupils to dilate. If the lesion is postganglionic, the sympathetically innervated effector cells become supersensitive to direct-acting sympathomimetics and, therefore, respond to weak and ordinarily ineffective concentrations of this drug (Figure 7).

Topical administration of one drop of 10 per cent phenylephrine[1] leads to mydriasis in the affected eye within five to 10 minutes (Figure 8). The ability of this pharmacologic test to differentiate a first or second-order (preganglionic) lesion remains controversial.

– **Parasympathetic denervation**

To test the ability of the pupil to constrict, two per cent pilocarpine[1] (a direct-acting parasympathomimetic) is installed into each eye (the affected eye and the control eye).

If the affected pupil remains dilated and the other pupil constricts, iris disease (mechanical restriction of the iris) or prior application of a mydriatic drug is likely (pharmacologic pupillary blockade due to atropine or atropine-like drugs). This pilocarpine[1] test is, therefore, not specific in its localising effect, but confirms that the lesion is neurologic (Figure 9).

However, if the affected pupil constricts sooner than the other pupil, a postganglionic lesion of the oculomotor nerve (ciliary ganglion or short ciliary nerves) is present, causing denervation supersensitivity.

A preganglionic lesion (parasympathetic nucleus of CNIII or the oculomotor nerve) can be evaluated by instilling 0.5 per cent physostigmine[1] (an indirect-acting parasympathomimetic) into

each eye.

If the affected pupil constricts before the control pupil, a preganglionic lesion is present. In case of postganglionic lesion, the affected pupil will not constrict (Figure 10).

Diseases associated with anisocoria

Aside from non-neurological causes (ocular disorder causing pain, glaucoma, iritis, iris degeneration etc), anisocoria can be caused by:

• unilateral lesion of the sympathetic supply to the eye (Horner's syndrome);

• unilateral lesion of the parasympathetic component of the oculomotor nerve (CNIII);

• cerebellar lesion;

• unilateral retinal or optic nerve lesion; and

• an acute brain disorder.

Criteria for differentiating these different causes are summarised in Table 1. Pupil abnormalities are common in acute brain disorders, such as head trauma and other conditions causing rapid change in intracranial pressure (intracranial bleed, decompensation from a brain tumour or inflammatory and/or infectious brain diseases).

In the absence of concurrent ocular trauma, miotic pupils may indicate loss of cortical input or direct damage to sympathetic centres in the diencephalon, allowing unopposed oculomotor pupillary constriction.

Pupils that are initially miotic and then become mydriatic and unresponsive to light are indicative of a progressive severe brainstem lesion (mostly seen with raised intracranial pressure and caudal subtentorial herniation).

Extensive lesions that affect the sympathetic innervation, as well as oculomotor nerve, result in mid-position fixed pupils.

• Items marked [1] are not licensed for dogs or cat use.

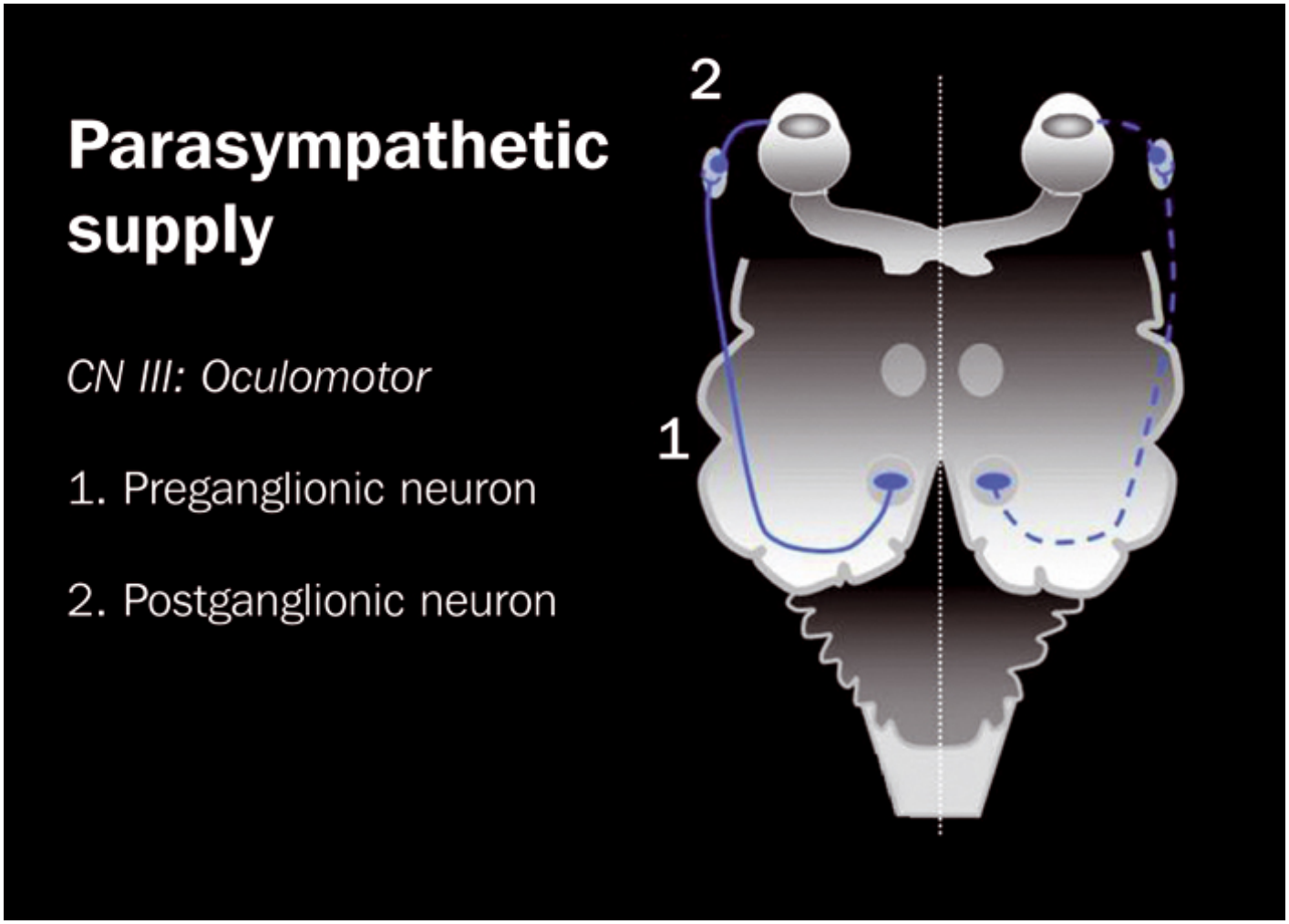

Figure 1. Parasympathetic supply to the eye. The ocular parasympathetic tract is a twoneuron pathway.

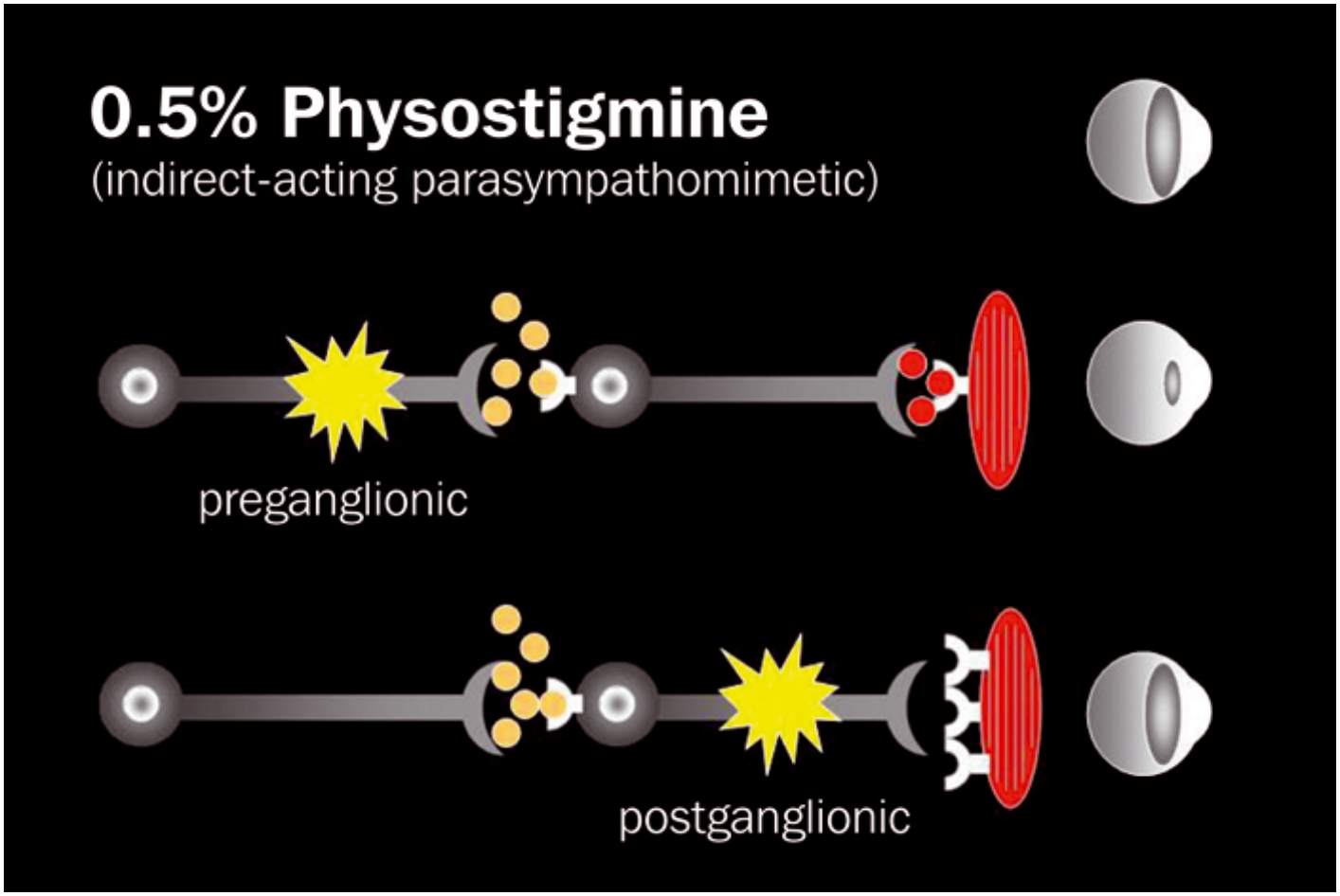

Figure 10. Determination of lesion localisation in a case of parasympathetic denervation by the physostigmine test.

Figure 2. Anisocoria due to parasympathetic denervation on the left eye.

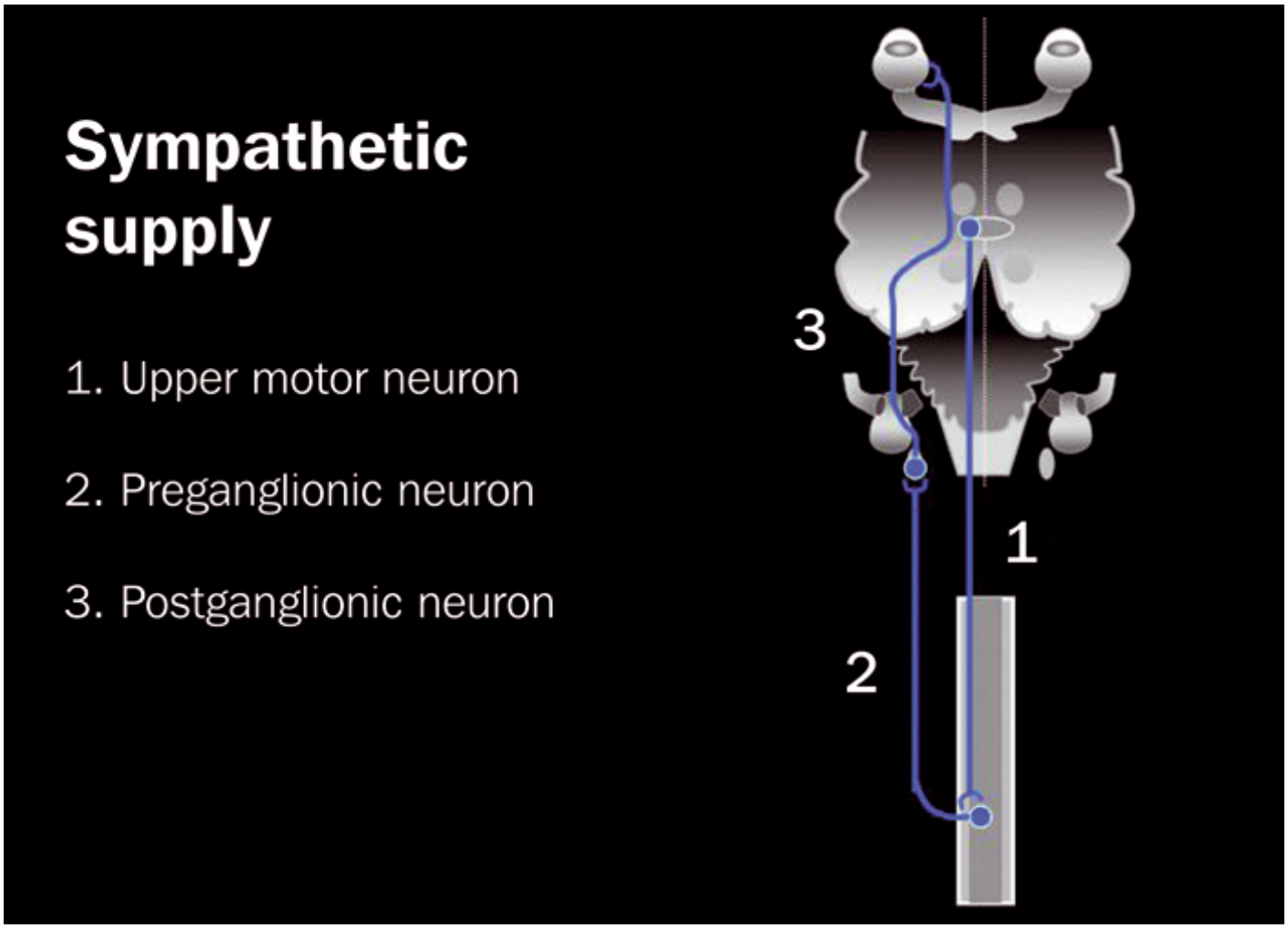

Figure 3. Sympathetic supply to the eye.

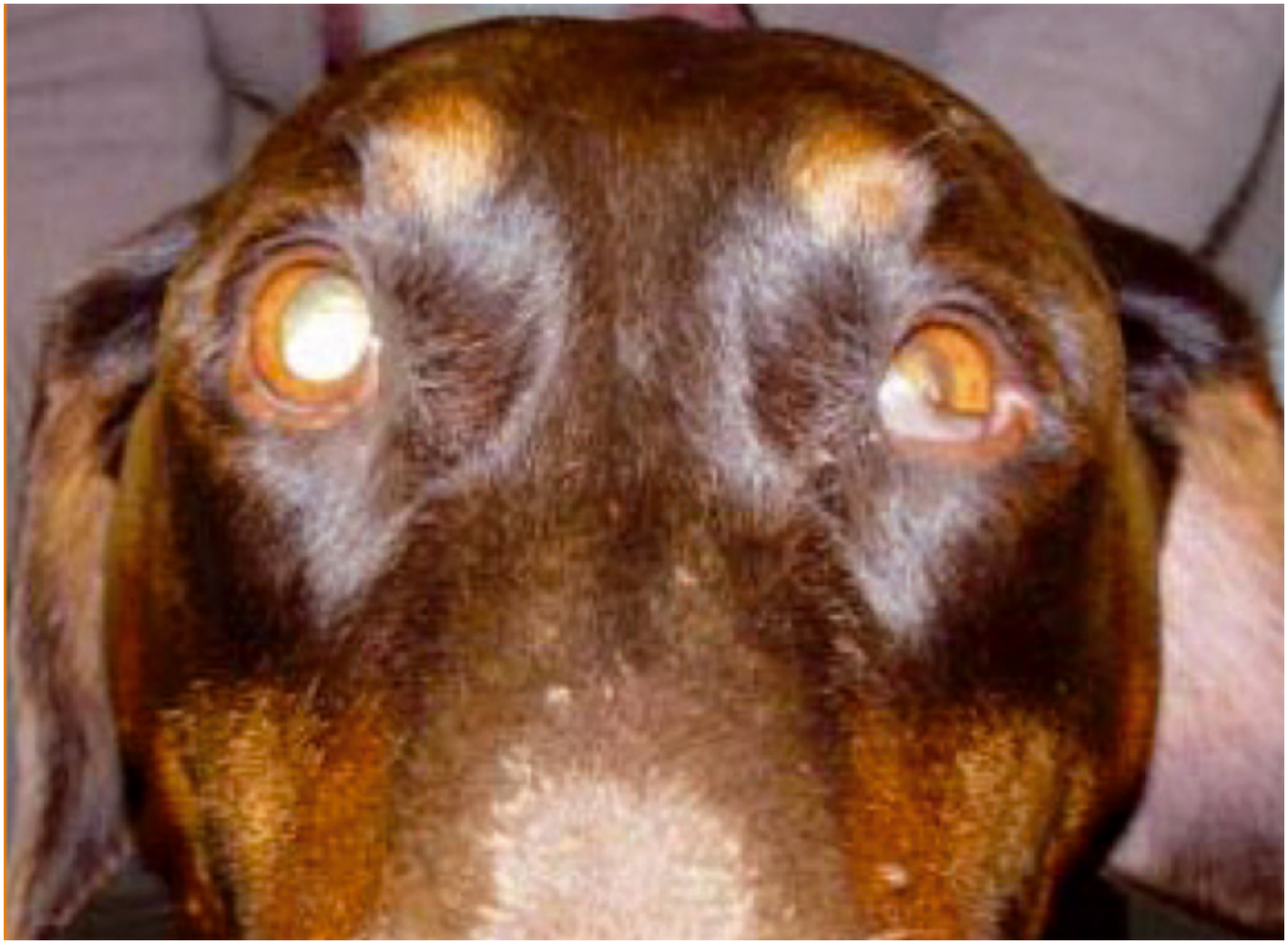

Figure 4. Horner's syndrome on the left eye.

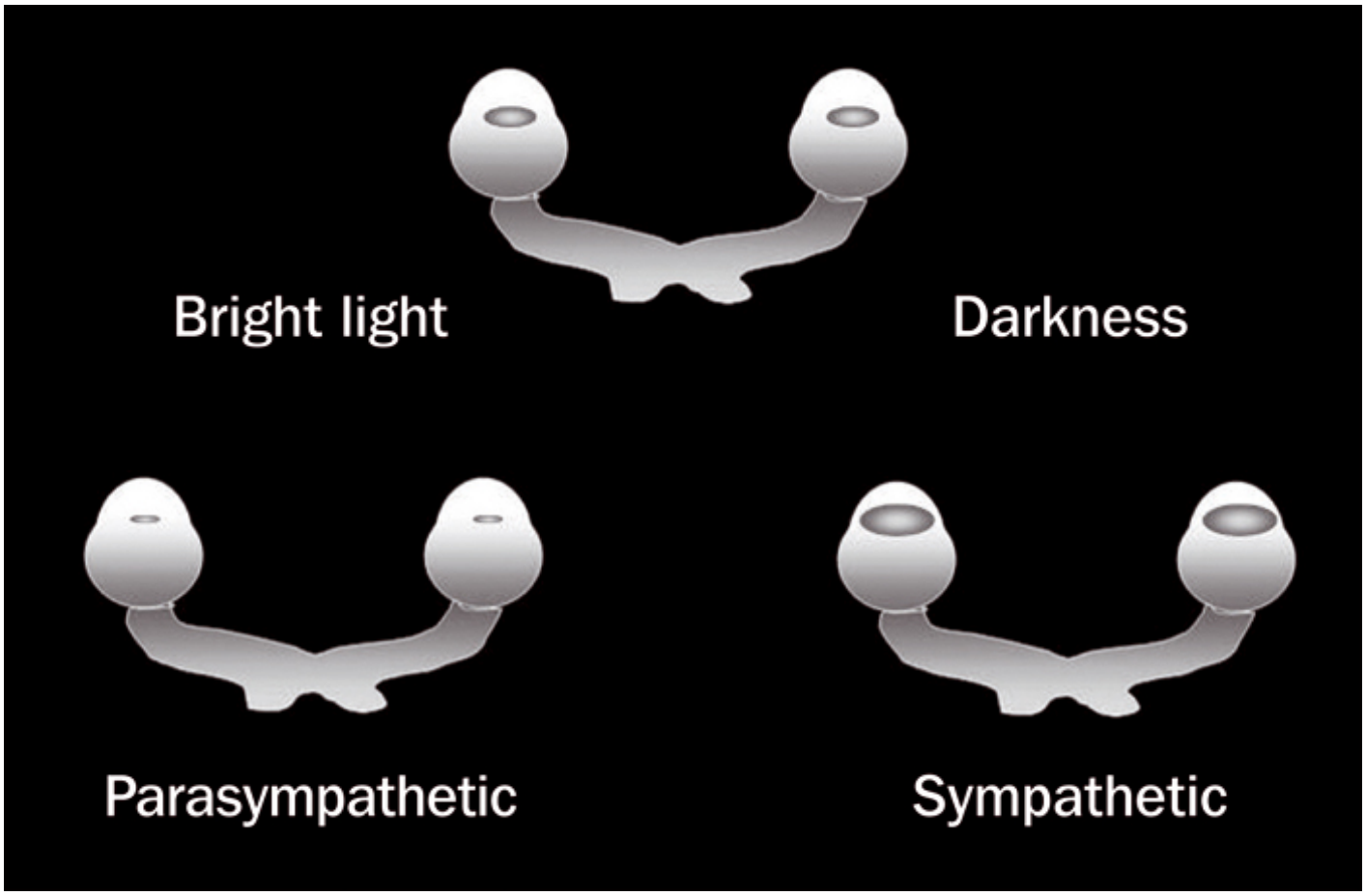

Figure 5. Evaluation of pupil size and symmetry.

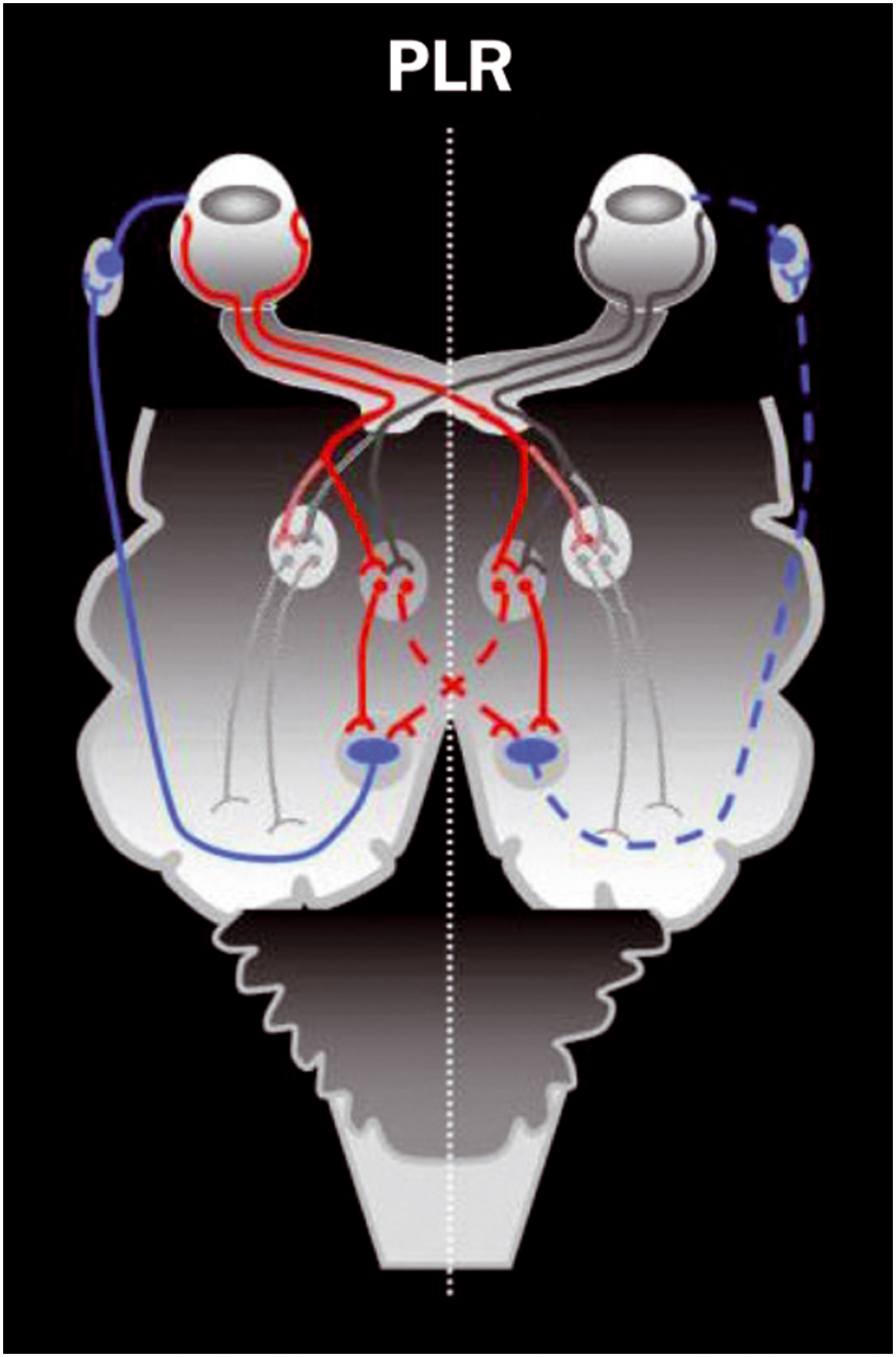
PLR

Figure 6. Pupillary light reflex (PLR) pathways. The axons of this second neurone innervate the iris and ciliary body musculature.

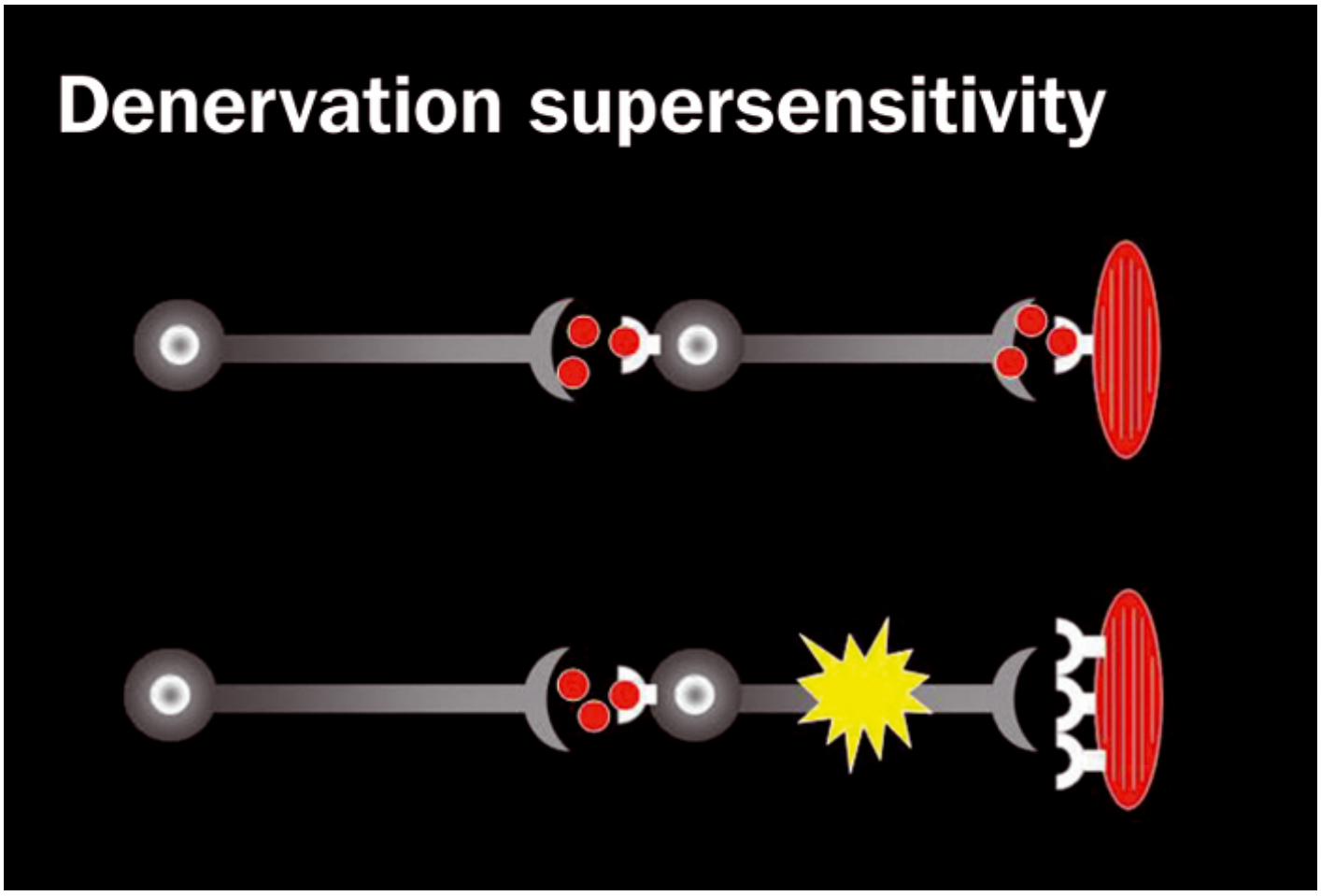

Figure 7. The principle of denervation supersensitivity.

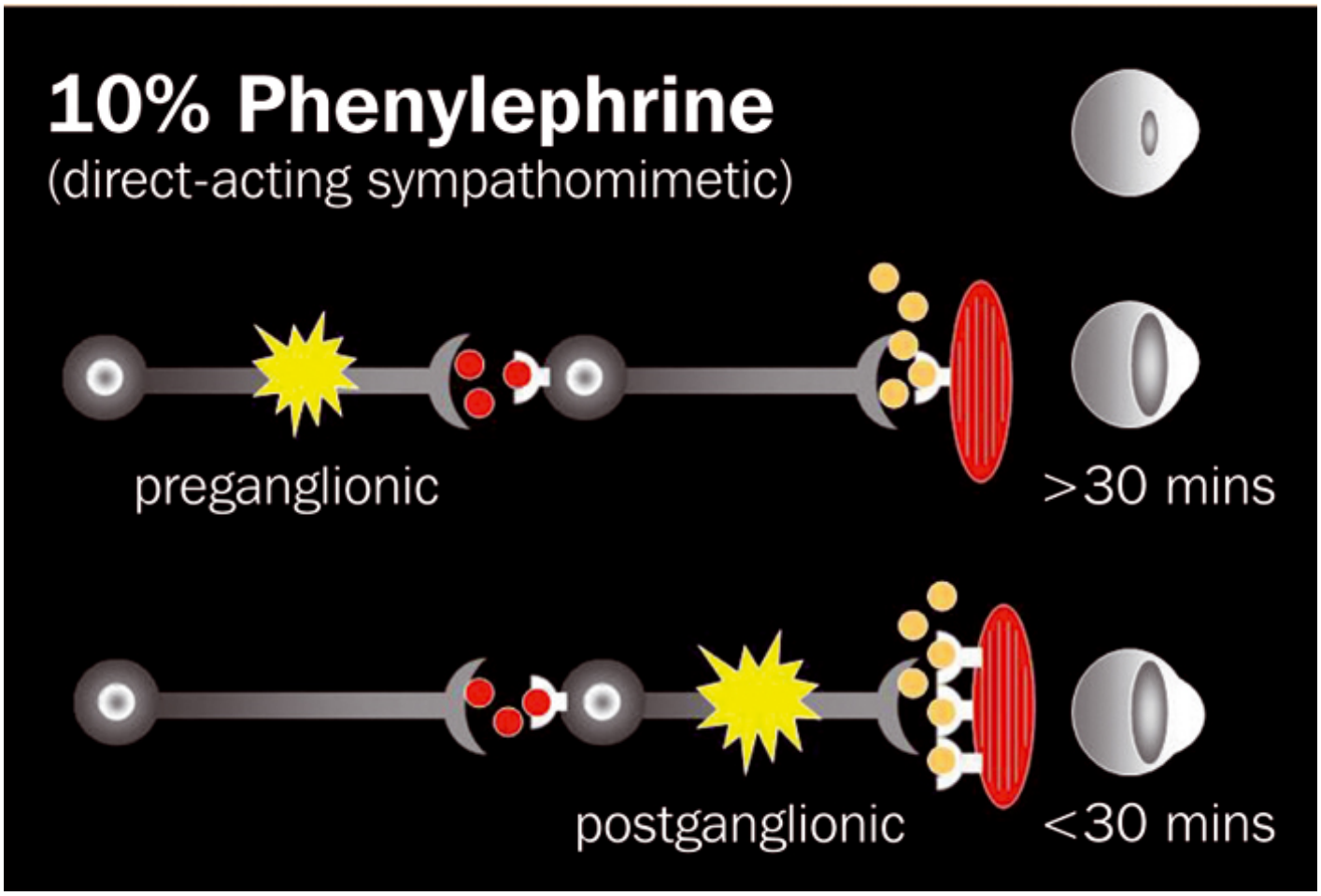

Figure 8. Evaluation of sympathetic denervation by the phenylephrine test. The ability of this pharmacologic test to differentiate a first or second-order (preganglionic) lesion remains controversial.

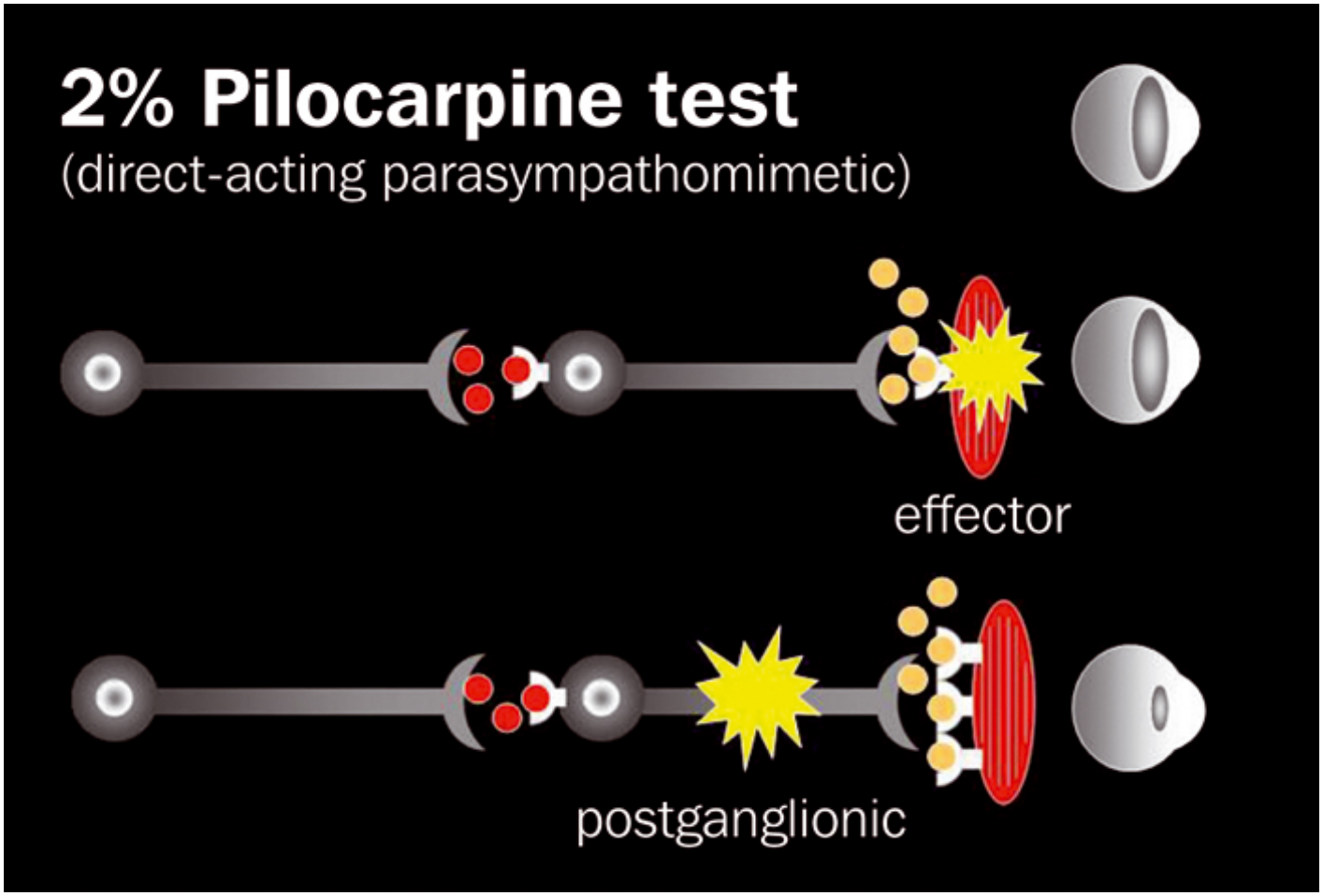

Figure 9. Evaluation of parasympathetic denervation by the pilocarpine test.

Lesion localisation	Pupil abnormality	Associated signs
Sympathetic supply to the eye (Horner's syndrome)	Miosis, intact PLR	Anisocoria worsens in darkness, third eyelid protrusion, enophthalmos, ptosis upper eyelid and normal vision
Parasympathetic component of oculomotor nerve (CNIII)	Severe mydriasis, absent direct and indirect PLR	Anisocoria worsens in light, narrowing of the palpebral fissure due to ptosis of upper eyelid, normal vision, ventrolateral strabismus and reduced ocular mobility if motor component of CNIII involved
Unilateral retinal lesion	Partial mydriasis, absent direct PLR, normal indirect PLR	Pupils symmetrically dilated in darkness, fundoscopic examination and the patient's vision is abnormal
Unilateral optic nerve lesion	Partial mydriasis, absent direct PLR, normal indirect PLR	Pupils symmetrically dilated in darkness and vision abnormal
Cerebellar lesion	Ipsilateral miosis or contralateral mydriasis	Menace deficit with normal vision, intention tremor, hypermetric gait and vestibular signs

Table 1. Causes of anisocoria