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Nonhypotensive autonomic agents in veterinary ophthalmology

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Anatomy and physiology of the autonomic nervous system

The autonomic nervous system is an involuntary motor system composed of the parasympathetic and sympathetic divisions, innervating secretory glands, cardiac muscle, and smooth muscle of blood vessels and viscera. Both divisions of the autonomic system have central and peripheral components. Higher centers for integration of the pars parasympathetica and pars sympathetica are located in the hypothalamus and reticular formation in the brain stem [1]. These neurons synapse with the lower motor neuron (LMN) of each division. In both divisions of the autonomic nervous system, the LMN is a two-neuron system (Fig. 1) [2]. The preganglionic neuron is located in the central nervous system (CNS), and synapses are located in a peripheral autonomic ganglion on the postganglionic neuron. The axon of the postganglionic neuron terminates at the effector organ. The LMN of the parasympathetic system arises from the nuclei of cranial nerves III, VII, IX, and X and the intermediolateral cell column of the first through third sacral spinal nerves in the dog and cat (craniosacral distribution). The LMN of the sympathetic system arises from the intermediolateral cell column of the eighth cervical through fifth lumbar spinal nerves (thoracolumbar distribution) [2,3].

Autonomic innervation to the eye and orbit consists of parasympathetic and sympathetic nervous pathways. Parasympathetic innervation to the structures of the orbit and salivary glands arises from the parasympathetic

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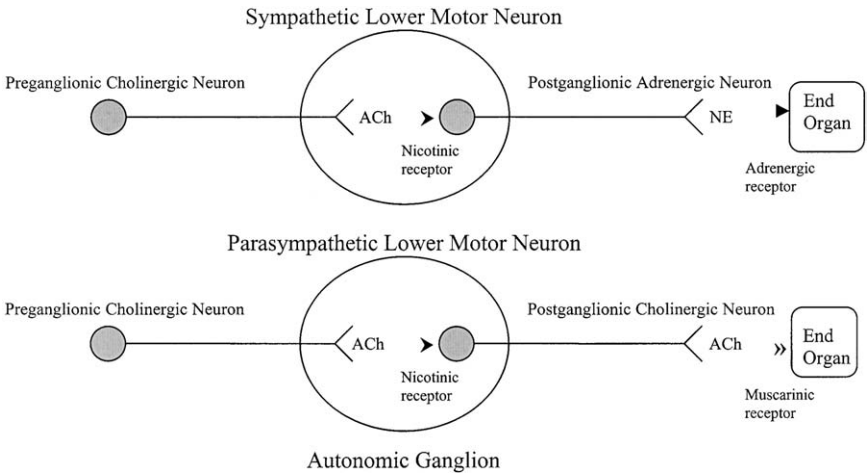

Fig. 1. Diagram of the lower motor neuron system of the pars sympathetica and pars parasympathetica of the systema nervosum autonomicum. The cell bodies of the preganglionic neurons of both divisions are located within the central nervous system. Autonomic ganglia (◯) are peripherally located. They are paravertebral and prevertebral in the sympathetic division and juxtavisceral and intramural in the parasympathetic division. Preganglionic neurons of both divisions are cholinergic. These neurons release the neurotransmitter acetylcholine (ACh) into the synaptic cleft, which binds to nicotinic receptors (➤) on the postganglionic neuron. The cholinergic parasympathetic postganglionic neuron releases ACh, which binds to muscarinic receptor (»») at the neuroeffector junction. Most sympathetic postganglionic neurons are adrenergic, releasing norepinephrine (NE) into the sympathetic cleft to bind to an adrenergic receptor (▶) at the neuroeffector.

nuclei of cranial nerves III, VII, and IX, and the fibers exit the CNS in their respective cranial nerves (Fig. 2) [2].

Parasympathetic preganglionic neurons of CN III are located in the ventral tegmental area and anteromedian nucleus, the rostral extension of the Edinger-Westphal nucleus [4,5]. These preganglionic fibers exit the CNS and synapse in the ciliary ganglion with the postganglionic neurons that innervate the iris sphincter and dilator muscles as well as the ciliary muscle (see Fig. 2). The postganglionic fibers enter the globe via five to eight short ciliary nerves in the dog and via two short ciliary nerves in the cat: the nasal and malar short ciliary nerves [6]. Cholinergic innervation to the iris sphincter, iris dilator, and ciliary muscles is documented in several species [7–9]. Parasympathetic activity results in miosis through a combination of excitatory cholinergic innervation to the iris sphincter muscle and inhibitory cholinergic innervation to the dilator muscle [8]. Parasympathetic stimulation causes ciliary muscle contraction. Lenticular accommodation occurs as the change in tension on lens zonules results in subsequent changes in lens curvature and position. Contraction of the ciliary muscle also enhances aqueous humor outflow facility to lower intraocular pressure (IOP). In primates, longitudinal ciliary muscle fibers insert on the scleral spur and

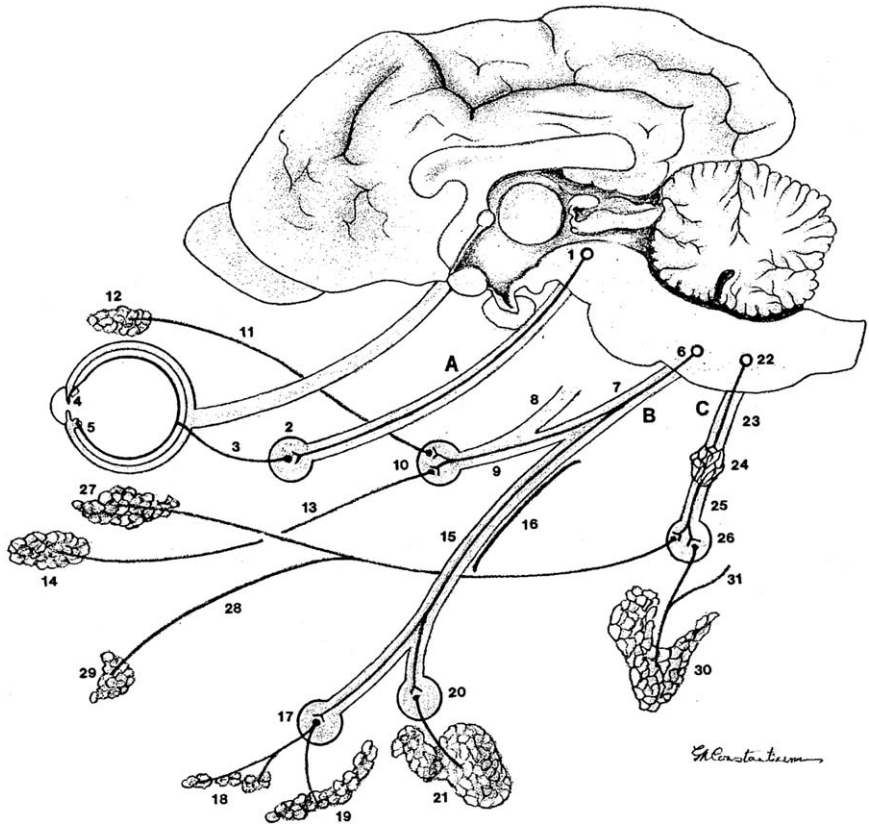

Fig. 2. Cranial parasympathetic innervation of the eye and the glands of the head in the dog. A, oculomotor n. (CNIII); B, facial n. (CNVII); C, glossopharyngeal n. (CNIX); 1, parasympathetic nucleus of CNIII; 2, ciliary ggl.; 3, short ciliary nn.; 4, sphincter m. of iris; 5, ciliary mn.; 6, parasympathetic nucleus of CNVII; 7, major petrosal n.; 8, deep petrosal n. (sympathetic); 9, n. of the pterygoid canal; 10, pterygopalatine ggl.; 11, postganglionic fibers to the lacrimal gland via the lacrimal nn.; 12, lacrimal gland; 13, postganglionic fibers to the nasal glands via the caudal nasal n.; 14, nasal glands; 15, chorda tympani n.; 16, lingual n. (from trigeminal n.); 17, sublingual ggl.; 18, polystomatic sublingual gland; 19, monostomatic sublingual gland; 20, mandibular ggl.; 21, mandibular gland; 22, parasympathetic nucleus of CNIX; 23, tympanic n.; 24, tympanic plexus; 25, minor petrosal n.; 26, otic ggl.; 27, zygomatic gland; 28, postganglionic fibers to the ventral buccal glands via the buccal n.; 29, ventral buccal glands; 30, parotid gland; 31, auriculotemporal n. carrying postganglionic fibers to the parotid gland.

contraction opens the drainage angle to decrease outflow resistance [10]. Most veterinary species lack a scleral spur, and the exact mechanism by which parasympathetic stimulation lowers IOP is not known.

The parasympathetic nucleus of CN VII, formerly the rostral salivatory nucleus, contains the cell bodies of preganglionic parasympathetic neurons [11]. These neurons exit the CNS in CN VII via the major petrosal n., which branches into the n. of the pterygoid canal and the chorda tympani n. The

axons of the n. of the pterygoid canal synapse in the pterygopalatine ganglion (see Fig. 2). Postganglionic fibers are distributed to the lacrimal gland via the lacrimal n. (from the ophthalmic n. of the trigeminal n.) and to the nasal glands via the caudal nasal n. (from the maxillary n. of the trigeminal n.). Postganglionic fibers innervating the acinar cells of the lacrimal gland regulate electrolyte and water secretion [12]. The axons of the chorda tympani n. carried by the lingual n. (from the mandibular n. of the trigeminal n.) synapse in the carnivores in two ganglia: sublingual and mandibular. From the former, the postganglionic fibers supply the sublingual salivary glands (monostomatic and polystomatic), whereas from the latter, the postganglionic fibers innervate the mandibular salivary gland.

Preganglionic fibers from neurons arising in the parasympathetic nucleus of CN IX, formerly the caudal salivatory nucleus, travel as the tympanic n. and synapse in the otic ganglion with the postganglionic neurons (see Fig. 2) [6,11]. The postganglionic fibers are distributed to three salivary glands: the zygomatic gland, the ventral buccal glands, and the parotid gland. The fibers for the ventral buccal glands reach the glands via the buccal n., whereas the fibers for the parotid gland reach the gland via the auriculotemporal n., both branches of the mandibular n. of the trigeminal n.

Preganglionic neurons of the pars sympathetica originate in the intermediolateral cell column of the first through third or fourth thoracic spinal cord segments [6]. The axons leave the CNS in the ipsilateral ventral nerve roots of the same spinal cord segment and travel in the ramus communicans to the sympathetic chain and thoracic sympathetic trunk. These neurons synapse on postganglionic neurons in the cranial cervical ganglion and travel rostrally with various blood vessels and cranial nerves to innervate the structures of the orbit. Most postganglionic sympathetic fibers are ultimately distributed to the structures of the head in branches of CN V. Some sympathetic fibers travel in the nasociliary n., a branch of the ophthalmic division of CN V, and innervate the smooth muscle of the periorbita, the orbitalis muscle, which functions to press the globe anteriorly and to retract the eyelids [13]. Additional fibers continue in the long ciliary n., a branch of the nasociliary n., and enter the globe to innervate smooth muscles of the iris and ciliary body as well as vascular smooth muscle of the uveal tract. Sympathetic innervation to Müller's muscle of the upper eyelid and to the smooth muscle of the third eyelid is carried by the infratrochlear n., a branch of the nasociliary n. Sympathetic innervation to these structures mediates pupillary dilation, vasoconstriction, elevation of the upper eyelid, and retraction of the third eyelid.

The lacrimal gland is innervated by both divisions of the autonomic nervous system. Parasympathetic innervation has already been described. Postganglionic sympathetic fibers are carried to the lacrimal gland in the lacrimal n., a branch of the ophthalmic n. of the trigeminal n [12]. Sympathetic fibers are distributed to the interstitium surrounding acini and to vascular smooth muscle fibers of the glands [12,14].

Preganglionic sympathetic fibers originating in the midthoracic spinal cord innervate the adrenal medulla, which is homologous to an autonomic ganglion. The preganglionic fibers synapse on adrenal chromaffin cells, modified postganglionic sympathetic neurons that release the catecholamines epinephrine and norepinephrine (NE) into systemic circulation [15].

Cholinergic and adrenergic receptors and neurotransmitters

Acetylcholine (ACh), NE, and epinephrine are the neurotransmitters used by both divisions of the autonomic nervous system. Neurons are classified by the neurotransmitter released by the nerve terminal; thus, neurons releasing ACh are called cholinergic neurons and those releasing NE are called adrenergic neurons (see Fig. 1). The preganglionic neurons of the sympathetic and parasympathetic divisions are cholinergic fibers. All parasympathetic postganglionic neurons are cholinergic. Most postganglionic neurons of the sympathetic nervous system are adrenergic. Certain sympathetic postganglionic neurons are cholinergic, namely, those innervating sweat glands in some species and vascular smooth muscle of skeletal muscles [15].

Cholinergic receptors are of two subtypes: nicotinic and muscarinic. ACh released into the synaptic cleft by cholinergic neurons activates nicotinic or muscarinic receptors on the postsynaptic membrane [15]. Nicotinic receptors are excitatory, and binding of neurotransmitter to the receptor causes depolarization of the postsynaptic cell. Autonomic ganglia of both divisions use nicotinic receptors on the postsynaptic membrane of the postganglionic neuron (see Fig. 1). Muscarinic receptors are present at the neuroeffector junction of organs innervated by postganglionic cholinergic neurons. Muscarinic receptor activation can be excitatory or inhibitory [16], for example, excitatory cholinergic receptors are located on the iris sphincter, whereas inhibitory cholinergic receptors are located on the iris dilator muscle in the dog [8]. ACh activity is blocked at nicotinic receptors by curare and curare-like drugs, whereas its activity at muscarinic receptors is blocked by atropine and atropine-like drugs. Rapid elimination of ACh within the synaptic cleft is a result of hydrolysis into choline and acetic acid by the enzyme acetylcholinesterase (AChE).

Postganglionic sympathetic adrenergic neurons release the neurotransmitter NE, which binds to α- and β-adrenergic receptors. Subtypes α_1, α_2, β_1, β_2, and β_3 exist and have been classified by the potency of various catecholamines at the receptor subtype [15]. Most α_1 receptors are primarily excitatory and are located at the postsynaptic motor endplate of smooth muscle. Excitatory α-adrenergic receptors have been identified in the iris dilator, iris sphincter, ciliary muscle, and vascular smooth muscle of the eye and orbit of various species [8,17,18]. The α_2 receptors are located at the presynaptic nerve endings, and binding of NE to α_2 receptors causes decreased release of neurotransmitter from the presynaptic terminal. The α_2

receptors are found in canine iris sphincter muscle, where they mediate smooth muscle relaxation for enhanced mydriasis [8], and in human iris epithelium, ciliary epithelium, and ciliary muscle [19]. Postjunctional α_2 receptors on the ciliary epithelium are believed to mediate inhibition of adenylate cyclase via an inhibitory G protein that suppresses aqueous humor production on α_2 receptor activation [20].

The β_1 receptors are located on cardiac muscle and gastrointestinal smooth muscle, where they have excitatory and inhibitory function, respectively. β_2 receptors are inhibitory and are found on bronchial and vascular smooth muscle. β_2 receptor activation mediates broncho- and vasodilation. Inhibitory β-adrenergic receptors are found on the iris sphincter muscle and ciliary muscle in a variety of species [8,18,21,22]. Pharmacologic inhibition of β-adrenergic receptors in the ciliary processes reduces blood flow and aqueous humor production [23].

Termination of NE activity at the neuroeffector junction occurs through three separate mechanisms: NE inactivation by the enzyme catechol-O-methyltransferase, diffusion away from the synapse, and neuronal reuptake into the presynaptic terminal.

After denervation of an effector organ by a destructive lesion to a parasympathetic or sympathetic postganglionic neuron, upregulation of postsynaptic receptors occurs; supersensitivity to exogenously administered neurotransmitter also occurs within 2 to 12 days [21,24,25]. This principle of denervation supersensitivity is the basis for pharmacologic localization of sympathetic denervation (eg, Horner's syndrome) and parasympathetic denervation (eg, internal ophthalmoplegia, dysautonomia) with autonomic drugs.

Cholinergic agents (parasympathomimetics)

Cholinergic agents, or parasympathomimetics, mimic the effects of ACh at muscarinic receptors. These drugs can be divided into the direct-acting agents that activate muscarinic receptors at postganglionic parasympathetic neuroeffector junctions and the indirect-acting agents that inhibit AChE to prolong the action of ACh at the synaptic cleft. These agents are commonly employed for pharmacologic testing of pupillomotor defects and in the treatment of glaucoma and keratoconjunctivitis sicca (KCS). The reader is directed elsewhere in this issue for a detailed discussion of cholinergic agents in the treatment of glaucoma.

Direct-acting cholinergic agonists

Direct-acting cholinergic agonists used in veterinary ophthalmology include the choline esters (acetylcholine and carbachol) and the natural alkaloid (pilocarpine). Through their actions at muscarinic receptors on iris and ciliary muscles and lacrimal glands, the effects of these drugs include

miosis, ciliary muscle contraction for lenticular accommodation, reduction of IOP, and increased lacrimation. Ocular side effects of these drugs include blepharospasm, conjunctival hyperemia, and transient breakdown of the blood–aqueous barrier, manifested as aqueous humor flare and ocular hypotony [26–28]. Systemic absorption of cholinergic drugs can result in signs of generalized increase in parasympathetic activity, such as ptyalism, emesis, diarrhea, and cardiac arrhythmias.

ACh is a quaternary nitrogen compound that is available for intraocular use (Table 1). Topical application has no effect on intraocular structures because of poor penetration of intact corneal epithelium and the presence of cholinesterases in the corneal stroma [29]. Intracameral injection of this agent results in rapid miosis of short duration and can be used after cataract surgery for reversal of mydriasis [30]. The short duration of action of ACh is the result of rapid hydrolysis by AChE within the iris and limits the usefulness of this drug.

Carbachol is a synthetic carbamyl ester of choline and, like acetylcholine, contains a quaternary nitrogen group. In addition to direct cholinergic agonism, carbachol has indirect cholinergic activity as an inhibitor of AChE [29]. Carbachol is resistant to cholinesterase activity and has a greater potency and longer duration of action than either ACh or pilocarpine. As a result of poor penetration of intact corneal epithelium, topical formulations contain a wetting agent, benzalkonium chloride, to enhance corneal penetration. Formulations are available for intraocular injection (0.01%) and topical application (0.75%–3%; see Table 1). The effects of carbachol include miosis, increase in aqueous outflow facility, and reduction in IOP [31]. Carbachol is indicated in the treatment of glaucoma and as a miotic after cataract surgery in dogs. Intracameral injection of 0.01% carbachol, 0.5 mL, after phacoemulsification can be used to prevent postoperative increases in IOP in dogs [32,33]. After implantation of an intraocular lens, carbachol-induced miosis also removes iris from the corneal incision, decreases the potential for peripheral anterior synechia, and stabilizes the position of the lens in the posterior chamber.

Pilocarpine hydrochloric acid (HCl) is a natural alkaloid produced from the leaves of Brazilian shrubs (*Pilocarpus* sp). Unlike other cholinergic agents, which are poorly lipid-soluble quaternary amines, pilocarpine contains a tertiary nitrogen group that facilitates corneal penetration. Pilocarpine is available in 0.25% to 10% solutions, 4% gel, as an ocular insert for prolonged release, and in combination with epinephrine HCl 1% (see Table 1).

Concentrations of 1% to 2% solution and 4% gel are most commonly used in veterinary medicine in the treatment of glaucoma. Cholinergic stimulation of ciliary muscle results in opening of the iridocorneal angle structures to enhance outflow facility. Muscarinic receptors have also been demonstrated within the trabecular meshwork of people [34]. The direct-acting muscarinic agonists pilocarpine and carbachol have been shown to

Table 1
Commercially available autonomic agents

Drug	Form supplied
Cholinergic agonists	
Direct acting	
Acetylcholine	Michol-E (Ciba Vision) 1:100 acetylcholine chloride when reconstituted in 2-mL dualchamber univial
Carbachol	Intraocular: Carbastat (Ciba Vision), Miostat (Alcon) 0.01% solution, in 1.5-mL vials. Topical: Isopto Carbachol (Alcon) 0.75%, 1.5%, 2.25%, 3%, Carboptic (Optopics) 3% solution, in 15- and 30-mL bottles
Pilocarpine HCl	Isopto Carpine (Alcon), Pilocar (Ciba Vision), Piloptic (Optopics), Pilostat (Bausch & Lomb), generics 0.25%, 0.5%, 1%, 2%, 3%, 4%, 6%, 8%, 10% solution, in 2-, 15-, and 30-mL bottles
	Pilopine HS (Alcon) 4% gel, in 3.5-g tubes
	Ocusert Pilo-20, Ocusert Pilo-40 (Alza) releases 20 μg/h and 40 μg/h for 1 week, respectively
	E-Pilo-1 (-2, etc; Ciba Vision), P1E1 (P2E1, etc; Alcon) epinephrine bitartrate 1% in combination with pilocarpine HCl (1%, 2%, 3%, 4%, or 6%) solution, in 10- and 15-mL bottles
Pilocarpine nitrate	Pilagan (Allergan) 1%, 2%, 4% solution, in 15-mL bottles
Indirect acting	
Reversible	
Demecarium bromide	Humorsol (Merck) 0.125% and 0.25% solution, in 5-mL bottles
Physostigmine	Isopto Eserine (Alcon) 0.5% solution no longer commercially available
Irreversible	Phospholine Iodide (Wyeth-Ayerst) powder for reconstitution: 1.5 mg to make 0.03%, 3 mg to make 0.06%, 6.25 mg to make 0.125%, 12.5 mg to make 0.25%, with 5 mL of diluent
Echothiophate iodide	Phospholine Iodide (Wyeth-Ayerst) powder for reconstitution: 1.5 mg to make 0.03%, 3 mg to make 0.06%, 6.25 mg to make 0.125%, 12.5 mg to make 0.25%, with 5 mL of diluent
Isofluorphate	Floropryl (Merck) 0.1% solution and 0.025% ointment no longer commercially available
Anticholinergics	
Atropine sulfate	Atrophate (Schering-Plough) 1%[a], various generic and trade names 0.5%, 1% ointment, in 3.5-g tubes
	Atropine care (Akorn), Isopto Atropine (Alcon), generics 0.5%, 1%, 2% solution, in 2-, 5-, and 15-mL bottles
Homatropine HBr	Isopto Homatropine (Alcon) 2%, 5%, AK-Homatropine (Akorn), generics 5% solution, in 1-, 2-, 5-, and 15-mL bottles
Cyclopentolate HCl	Cyclogyl (Alcon) 0.5%, 1%, 2%, AK-Pentolate (Akorn), Pentolair (Bausch & Lomb), generics 1% solution, in 2-, 5-, and 15-mL bottles
	Cyclomydril (Alcon) 0.2% solution in combination with 1% phenylephrine HCl, in 2- and 5-mL bottles

Table 1 (*continued*)

Drug	Form supplied
Scopolamine HBr	Isopto Hyoscine (Alcon) 0.25% solution, in 5- and >15-mL bottles Murocoll-2 (Bausch & Lomb) 0.3% solution in combination with 10% phenylephrine HCl, in 5-mL bottles
Tropicamide	Mydriacyl (Alcon), Opticyl (Optopics), Tropicacyl (Akorn), generics 0.5%, 1% solution, in 2- and 15-mL bottles Paremyd (Akorn) 0.25% solution in combination with hydroxyamphetamine HBr 1%, in 5- and 15-mL bottles
Adrenergic agonists	
Apraclonidine HCl	Iopidine (Alcon) 0.5% in 5- and 10-mL bottles, 1% solution, in 0.1-mL vials
Brimonidine tartrate	Alphagan (Allergan) 0.2%, Alphagan P (Allergan) 0.15% solution, in 5-, 10-, and 15-mL bottles
Dipivefrin HCl (Dipvalyl epinephrine)	Propine (Allergan), AKPro (Akorn), generics 0.1% solution, in 2-, 5-, 10-, and 15-mL bottles
Epinephrine borate	Epinal (Alcon) 0.5%, 1%, Eppy/N (Pilkington/Barnes-Hind) 1% solution, in 7.5-mL bottles
Epinephrine HClv	Epifrin (Allergan) 0.5%, 1%, 2%, solution, in 15-mL bottles, Glaucon (Alcon) 1%, 2% solution, in 10-mL bottles E-Pilo-1 (-2, etc; Ciba Vision), P1E1 (P2E1, etc; Alcon) epinephrine bitartrate 1% in combination with pilocarpine HCl (1%, 2%, 3%, 4%, or 6%) solution, in 10- and 15-mL bottles
Phenylephrine HCl	Mydfrin (Alcon), Phenoptic (Optopics) 2.5%, AK-Dilate (Akorn), Neo-Synephrine (Sanofi Winthrop), generics 2.5%, 10% solution, in 2-, 5-, and 15-mL bottles
Indirect-acting sympathomimetics	
Cocaine	Not commercially available
Hydroxyamphetamine HBr	Paremyd (Akorn) 1% in combination with tropicamide 0.25%, in 5- and 15-mL bottles, Paredrine (Smith-Kline Beecham) 1% solution, no longer commercially available
Adrenergic antagonists	
Betaxolol HCl	(Alcon) 0.5%, Betoptic S (Alcon), generics 0.25% solution, in 2.5-, 5-, 10-, and 15-mL bottles
Carteolol HCl	Ocupress (Ciba Vision), generics 1% solution, in 5-, 10-, and 15-mL bottles
Metipranolol HCl	OptiPranolol (Bausch & Lomb) 0.3% solution, in 5- and 10-mL bottles
Levobunolol HCl	Betagan Liquifilm (Allergan), AK-Beta (Akorn), generics 0.25%, 0.5% solution, in 2-, 5-, 10-, and 15-mL bottles
Levobetaxolol HCl	Betaxon (Alcon) 0.5% solution, in 5-, 10-, and 15-mL bottles
Timolol maleate	Timoptic (Merck), Betimol (Ciba Vision), generics 0.25%, 0.5% solution, in 2.5-, 5-, 10-, and 15-mL bottles
Dapiprazole HCl	Rev-Eyes (Bausch & Lomb) 0.5% solution when reconstituted, 25 mg of lyophilized powder with 5 mL of diluent in vial

Abbreviation: HCl, hydrochloric acid.

[a] Veterinary Approved Product.

Data from Plumb DC. Veterinary drug handbook. 4th edtion. Ames (IA): Iowa State Press; 2002; Bartlett JD. Ophthalmic drug facts 2003. St. Louis (MO): Facts and Comparisons; 2003; and Rhee DJ, Rapuano CJ, Weisbecker CA, Fraunfelder FT, editors. Physicians desk reference for ophthalmic medicine. 31st edition. Montvale (NJ): Thomson Medical Economics; 2002.

increase outflow facility through direct activity in the outflow pathway cells in the absence of ciliary muscle [35]. For a detailed description of pilocarpine use in this disease, the reader is directed elsewhere in this issue.

Blepharospasm and conjunctival hyperemia are observed after topical application; however, these effects diminish after 3 to 4 days [36]. Topical application of pilocarpine results in a transient increase in blood–aqueous barrier permeability [28,37]. The exact mechanism by which muscarinic agonists reduce blood–aqueous barrier permeability is unknown, but proposed mechanisms include increased permeability of ciliary epithelium [38], increased permeability of ciliary and iridal vascular endothelium [39], and vasodilation of anterior uveal blood vessels [40]. The breakdown of the blood–aqueous barrier by pilocarpine has been shown to be mediated in part through the corneal trigeminal reflex, in which corneal nerve stimulation results in neuropeptide release with subsequent production of inflammatory cytokines [37,41]. In dogs administered topical pilocarpine, aqueous humor flare and hypotony are inhibited by topical anesthetic, which blocks sensory stimulation of corneal nerves, and by topical nonsteroidal anti-inflammatory drugs, which block inflammatory cytokine production [37].

Pilocarpine has been recommended for use in the treatment of hyphema to enhance aqueous outflow through opening of the iridocorneal angle [42], although pilocarpine did not enhance red cell clearance in experimentally induced hyphema in rabbits [43]. Potential complications from pilocarpine therapy include potentiation of uveitis and formation of posterior synechia and iris bombé.

Pilocarpine can be administered for its lacrimogenic effects; however, its use has been widely supplanted by ophthalmic cyclosporine for the treatment of KCS. Pilocarpine is indicated in the treatment of KCS resulting from parasympathetic denervation of the lacrimal gland. Its effectiveness is dependent on the presence of some functional lacrimal gland; thus, it is not efficacious in cases of absolute KCS. Topical administration of 2% pilocarpine diluted in artificial tears, gentamicin, and acetylcysteine to a final concentration of 0.25%, has been advocated for the treatment of KCS [44]; however, no lacrimostimulatory effects were observed with topical 0.25%, 1%, or 2% pilocarpine in normal dogs in one study [45]. Systemic administration of pilocarpine nitrate orally at a dose of 2 to 4 mg/d has been reported [46]. To evaluate response, the drug should be administered for a period of 4 to 6 weeks. Currently, oral administration of 1% to 2% pilocarpine ophthalmic solution is recommended at an initial dose of one drop per 10 kg of body weight in food twice daily. Subsequent doses are increased by one drop until signs of systemic toxicity are observed and are then lowered to the previously tolerated dose [47]. Systemic signs of pilocarpine toxicity observed with higher doses include hypersalivation, vomiting, diarrhea, and cardiac arrhythmias. Concurrent administration of other parasympathomimetics, such as organophosphates or carbamate

antiparasitic agents, should be avoided to prevent potentiation of adverse effects.

Dysautonomia is a disease of the dog and cat characterized by generalized dysfunction of the autonomic nervous system. Ocular signs of dysautonomia include mydriasis, xerophthalmia, and prolapse of the nictitating membrane (Haws). Clinical signs can be treated with one drop of ophthalmic pilocarpine 0.25% to 1% to one or both eyes every 12 to 24 hours [48]. In cats with Haws caused by dysautonomia, retraction of the nictitating membrane occurs in response to pilocarpine administration [49], and although the smooth muscle of the feline third eyelid is sympathetically innervated, it responds to AChE, histamine, and direct-acting sympathomimetics [41,50].

Pilocarpine is useful in the diagnosis and neuroanatomic localization of anisocoria or bilateral mydriasis caused by parasympathetic dysfunction. The affected eye(s) is(are) mydriatic, there is an absent or slow pupillary light reflex (PLR), and anisocoria, if present, is more pronounced in bright light. Afferent PLR lesions have similar signs and can be distinguished from the former by the presence of visual deficits. Causes of parasympathetic dysfunction include internal ophthalmoplegia (paralysis of intraocular muscles), dysautonomia, and pharmacologic blockade by muscarinic agonists, such as atropine, jimsonweed, and deadly nightshade [51].

Pharmacologic testing of parasympathetic lesions should be performed with pilocarpine and physostigmine, an indirect-acting cholinergic agent, 24 hours apart [52]. In testing of unilateral lesions, both eyes should be treated, whereas only one eye is treated when testing bilateral disease. One drop of topical pilocarpine diluted to 0.1% has no effect on a normal pupil in the dog or cat. If miosis occurs after administration of one drop of pilocarpine 0.1%, supersensitivity of the iris sphincter muscle because of a postganglionic parasympathetic lesion is confirmed [53]. If no response is observed, a single drop of pilocarpine 2% can be administered to distinguish neurologic causes of mydriasis from primary iris lesions or pharmacologic blockade of iris sphincter muscle. In cases of primary iris disease or pharmacologic blockade, the affected pupil does not constrict or constricts incompletely and more slowly than the control pupil [6]. A quicker and more complete response of the affected eye to pilocarpine 2% confirms a neurologic lesion but does not allow neuroanatomic localization to central, preganglionic, or postganglionic lesions.

Indirect-acting cholinergic agonists

Indirect-acting cholinergic agonists prolong the effects of ACh by inhibiting AChE. This class of drugs is divided into the reversible AChE inhibitors physostigmine and demecarium bromide and the irreversible AChE inhibitors isofluorphate and echothiophate iodide. Ocular effects of the anticholinesterases include miosis, accommodation, and lowering of IOP

through facilitation of aqueous humor outflow. As a result, these drugs are most commonly employed in the treatment of glaucoma [54]. Similar to the direct-acting cholinergics, topical administration of anticholinesterases results in vasodilation, increased capillary permeability of the iris and ciliary body, and breakdown of the blood–aqueous barrier [28,55]. Additional ocular complications in people include formation of iris cysts (particularly in children), retinal detachment, and development of lens opacities [55,56]. Systemic side effects of these drugs are a result of widespread cholinergic activity and include skeletal muscle weakness, bradycardia, hypotension, hypersalivation, vomiting, and diarrhea [16,57]. Treatment with atropine, a competitive ACh antagonist, improves clinical signs of side effects, including those induced by the irreversible AChE antagonists. Administration of the cholinesterase inhibitors should be performed with caution in patients receiving other organophosphate or carbamate parasiticides, edrophonium for treatment of myasthenia gravis, or succinylcholine for paralysis during general anesthesia [58].

Demecarium bromide and physostigmine are carbamates that reversibly antagonize AChE by carbamylating the enzyme at its esteratic site. Hydrolysis of the complex regenerates the active enzyme. Demecarium bromide is available in 0.125% and 0.25% solutions (see Table 1). Demecarium is a potent miotic and lowers IOP. A single dose induces miosis for 49 to 77 hours and reduces IOP for 49 to 55 hours in normal and glaucomatous Beagles [54].

Physostigmine is an alkaloid derived from the seed of a West African vine (*Physostigma venenosum*). A 0.5% solution is no longer commercially available (see Table 1). Physostigmine is useful in pharmacologic testing and neuroanatomic localization of anisocoria caused by a suspected parasympathetic lesion. Testing with an indirect-acting cholinomimetic, such as physostigmine, should precede pilocarpine testing by 24 hours [53]. Physostigmine 0.5% is administered to one or both eyes in cases of bilateral or unilateral disease, respectively. In central and preganglionic parasympathetic lesions, the response of the affected pupil is faster and to a greater degree than the response of the control pupil. In these cases, physostigmine potentiates the activity of ACh released from the intact postganglionic neuron at the nerve terminal. In lesions of the postganglionic neuron, there is no release of ACh at the neuroeffector terminal; thus, physostigmine does not induce miosis. In the case of a unilateral lesion, if neither pupil responds, the test has a provided false-negative result. Sufficient drug should be administered to both eyes to induce miosis in the control eye, because this test is not dependent on the phenomenon of denervation hypersensitivity [6].

Isofluorphate and echothiophate iodide are long-acting organophosphate compounds and potent cholinergic agents indicated in the treatment of glaucoma. Organophosphates antagonize AChE by phosphorylation of the esteratic site and form a stable enzyme-inhibitor complex that cannot

dissociate [16]. Isofluorphate is no longer commercially available. Echothiophate iodide, or phospholine iodide, is available in 0.03% to 0.25% solutions (see Table 1). In normal and glaucomatous Beagles, a single dose of echothiophate iodide 0.125% and 0.25% induced miosis for up to 55 hours and reduced IOP for up to 53 hours [54]. Echothiophate 0.25% can be used in the treatment of canine and equine ocular onchocerciasis and thelaziasis at a frequency of two to four times daily for 1 to 4 weeks [59,60]. Care must be taken to monitor for systemic toxicity if this therapy is selected for use in dogs. Pralidoxime (pyridine-2 aldoxime methiodide [2-PAM]) is an effective antidote for organophosphate toxicity and can be administered in conjunction with atropine. Pralidoxime removes the phosphate moiety at the AChE esteratic site to regenerate the active enzyme.

Anticholinergic agents (parasympatholytics)

The anticholinergic agents, or parasympatholytics, are reversible muscarinic antagonists and consequently inhibit the effects of ACh at the iris sphincter and ciliary muscles. Thus, the parasympatholytics are mydriatics and cycloplegics. The sympathomimetics epinephrine and phenylephrine are mydriatics through their stimulation of iris dilator muscle via α-adrenergic receptors but have few to no cycloplegic effects [61]. The relative efficacy of the mydriatic/cycloplegic agents has been examined in dogs, cats, horses, and cattle (Tables 2–5) [62–65]. Mydriatics/cycloplegics are used in

Table 2
Mydriatics in the dog

Drug	Maximum dilation (h)	Duration of action (h)	Comments
Atropine 1%	1	96–120	Maximum mydriasis, salivation, vomition
Atropine 4%	0.75	96–120	Maximum mydriasis, salivation, chemosis
Cyclopentolate 1%	0.75	60	Maximum mydriasis, chemosis
Homatropine 2%	0.75	48	Moderate mydriasis, salivation
Homatropine 5%	0.75	48	Moderate mydriasis, salivation, chemosis
Scopolamine 0.25%	0.75	96–120	Maximum mydriasis
Tropicamide 1%	0.5	12	Maximum mydriasis
Cocaine 4%			No mydriasis
Hydroxyamphetamine HBr 1%			No mydriasis
Epinephrine HCl 0.1%			No mydriasis
Phenylephrine 10%	2	12–18	Maximum mydriasis
Phenylephrine 10% + cyclopentolate 1%	0.75	24	Maximum mydriasis

Abbreviation: HCl, hydrochloric acid.

Adapted from Rubin LF, Wolfes RL. Mydriatics for canine ophthalmoscopy. J Am Vet Med Assoc 1962;140(2):137–41.

Table 3
Mydriatics in the cat

Drug	Maximum dilation (h)	Duration of action (h)	Comments
Atropine 1%	1	60	Maximum mydriasis, salivation, vomition
Atropine 4%	0.5	144	Maximum mydriasis, salivation, vomition
Cyclopentolate 1%	0.5	66	Maximum mydriasis, salivation
Cyclopentolate 2%	0.5	108	Maximum mydriasis, salivation
Homatropine 2%	0.75	10	Incomplete mydriasis, salivation
Tropicamide 0.5%	0.25	8–9	Maximum mydriasis, salivation
Tropicamide 1%	0.25	8–9	Maximum mydriasis, salivation
Epinephrine HCl 2%			No mydriasis
Phenylephrine 10%			No mydriasis
Phenylephrine 10% + atropine 1%	1	120	Maximum mydriasis, salivation
Phenylephrine 10% + cyclopentolate 1%	0.5	108	Maximum mydriasis, salivation
Phenylephrine 10% + homatropine 2%	1	24	Moderate mydriasis, salivation

Abbreviation: HCl, hydrochloric acid.

Adapted from Gelatt KN, Boggess TS, Cure TH. Evaluation of mydriatics in the cat. J Am Anim Hosp Assoc 1973;9:283–7.

ophthalmology for facilitation of the ophthalmic examination, for limiting posterior synechia and alleviating ciliary muscle spasm associated with uveitis, and for stabilization of the blood–aqueous barrier.

Atropine sulfate is a direct-acting anticholinergic agent derived from the deadly nightshade plant (*Atropa belladonna*). Belladonna alkaloids consist of atropine and scopolamine as well as the structurally related semisynthetic analogue of atropine, homatropine [27]. Atropine is a selective, reversible,

Table 4
Mydriatics in the horse

Drug	Onset of dilation (h)	Maximum dilation (h)	Duration of action (h)	Comments
Atropine 1%	0.75	10	132	Maximum mydriasis
Atropine 3%	0.5	12	264	Maximum mydriasis
Cyclopentolate 1%	0.5	12	96	Maximum mydriasis
Cyclopentolate 2%	0.25	12	120	Maximum mydriasis
Homatropine 2%	1	3	8	Moderate mydriasis
Scopolamine 0.25%	0.5	4	108	Maximum mydriasis
Tropicamide 0.5%	0.5	1	5	Maximum mydriasis
Tropicamide 1%	0.25	5	12	Maximum mydriasis
Phenylephrine 10%				No mydriasis
Phenylephrine 10% + atropine 1%	0.75	8	84	Maximum mydriasis

Adapted from Gelatt KN, Gum GG, MacKay EO. Evaluation of mydriatics in horses. Vet Comp Ophthalmol 1995;5(2):104–8.

Table 5
Mydriatics in cattle

Drug	Onset of dilation (h)	Maximum dilation (h)	Duration of action (h)	Comments
Atropine 1%	0.5	0.75	24	Maximum mydriasis
Atropine 3%	0.25	2	168	Maximum mydriasis
Cyclopentolate 1%	0.75	12	48	Maximum mydriasis
Cyclopentolate 2%	0.5	12	96	Maximum mydriasis
Homatropine 2%	0.75	6	48	Moderate mydriasis
Scopolamine 0.25%	0.5	2	144	Maximum mydriasis
Tropicamide 1%	0.25	0.75	3	Incomplete mydriasis
Tropicamide 0.5%	0.5	3	8	Incomplete mydriasis
Phenylephrine 10%				No mydriasis
Phenylephrine 10% + atropine 1%	0.5	2	24	Maximum mydriasis

Adapted from Gelatt KN, Gum GG, MacKay EO. Evaluation of mydriatics in cattle. Vet Comp Ophthalmol 1995;5(2):46–9.

muscarinic receptor antagonist [16]. Atropine is available in 0.5% to 2% solutions and in 0.5% and 1% ointments (see Table 1).

Topical administration results in pharmacologic blockade of the muscarinic receptors of the sphincter muscle of the iris and of the ciliary body musculature to effect pupillary dilation and cycloplegia. Mydriasis is attained earlier and with lower concentrations than cycloplegia, which requires higher concentrations or longer duration of administration. Atropine binds to uveal melanin and may act as a slow-release depot, resulting in slower onset and prolonged duration of mydriasis and cycloplegia in heavily pigmented eyes [66–68]. Maximum mydriasis is observed after topical administration of 1% to 4% atropine within 30 to 60 minutes in dogs, cats, and cattle and within 10 to 12 hours in horses (see Tables 2–5) [62–65]. Duration of mydriasis is prolonged in most veterinary species, lasting up to 264 hours after a single dose of 3% atropine in the horse [63]. Mydriasis may be evident up to 10 days after the last dose in dogs [69].

Atropine stabilizes the blood–aqueous barrier, decreasing permeability of blood vessels to proteins and intravenously administered fluorescein [70,71]. Topical atropine is indicated in the treatment of uveitis to attain mydriasis, limit posterior synechiation, and relieve painful ciliary muscle spasm. Topical therapy is initiated two to eight times daily to attain pupillary dilation and then once every 24 to 48 hours to maintain mydriasis [69,72]. Higher concentrations of up to 4% or combined administration with phenylephrine 10% may be necessary to obtain mydriasis in cases of active iridocyclitis [73]. Atropine is often used in the preoperative preparation for cataract surgery or other intraocular surgery in which mydriasis is beneficial [74].

Atropine is indicated in the initial treatment of hyphema to reduce permeability of the blood–aqueous barrier and to prevent posterior synechia; however, the IOP should be monitored, because mydriasis may exacerbate reduced aqueous outflow from accumulated red blood cells and

inflammatory cells [72]. Because the dilated iris impedes aqueous humor outflow, topical anticholinergic agents can cause elevation of IOP in human beings [75,76]. Shorter acting mydriatics may be beneficial in cases of uveitic glaucoma, in which pupillary mobility assists in the prevention and breakdown of posterior synechiae [77].

Atropine is a bitter substance, and hypersalivation may be observed as the solution travels down the nasolacrimal duct and is tasted. Ointment formulations may avoid this side effect and are especially useful in cats, in which hypersalivation is a common and often dramatic response observed after topical administration of atropine solution [62,78]. Direct application of a bitter substance to the tongue, such as a 1% atropine solution, can be used as a diagnostic tool to assess salivary flow from the parotid papilla in presurgical evaluation of parotid duct transposition for refractory cases of KCS [47]. As a result of parasympathetic inhibition at the lacrimal gland, decreased tear production in dogs occurs with systemic and topical administration [79,80]. In dogs, once-daily administration of a 1% solution topically for 2 weeks caused significant reduction in tear production within 2 hours of initial administration, and this persisted for 5 weeks after the last treatment [80]. Episodes of hallucinations and bizarre behavior in human beings and of compulsive circling in dogs have been reported after administration of topical atropine [81,82]. In the equine patient, systemic toxicosis caused by prolonged or frequent administration can result in decreased gut motility and signs of colic [83,84].

Tropicamide is a synthetic antimuscarinic agent and is available in 0.5% to 1% solutions and as a 0.25% solution in combination with 1% hydroxyamphetamine (see Table 1). Tropicamide is the mydriatic of choice for ophthalmic examination because of its rapid intraocular penetration, early onset of mydriasis, and short duration of action (see Tables 2–5) [62–65]. Tropicamide is a more potent mydriatic than cycloplegic drug [61]. As a result, tropicamide is less effective in relief of ciliary muscle spasm associated with uveitis than atropine. Similar to atropine, tropicamide reduces the permeability of the blood–aqueous barrier and can be beneficial in the treatment of uveitis [26]. Like atropine, topical application may also cause salivation in cats, but this effect is less severe with a lower concentration (0.5%) [62]. Mydriatics may cause elevation of IOP in human beings, [75,76] and increased IOP was observed in the treated and control eyes of normal cats after topical administration of tropicamide 0.5% [85]. In contrast, no significant changes in IOP were documented with the topical use of 0.5% and 1% solutions in normal dogs [86,87].

Homatropine HBr is a semisynthetic antimuscarinic agent structurally related to atropine; however, it is less effective as a mydriatic/cycloplegic with a shorter duration of action (see Tables 2–5) [62–65]. Homatropine is available in 2% and 5% solutions (see Table 1).

Scopolamine HBr is a naturally occurring belladonna alkaloid derived from the plant *Hyoscyamus niger*. Scopolamine is as effective as atropine as

a mydriatic/cycloplegic agent, with similar duration of action in those species studied (see Tables 2, 4, and 5) [63–65]. Scopolamine is available as a 0.25% solution and as a 0.3% solution in combination with 10% phenylephrine (see Table 1).

Cyclopentolate HCl is a synthetic anticholinergic and potent mydriatic/cycloplegic with prolonged duration of action. It is available in 0.5% to 2% solutions and as a 0.2% solution in combination with 1% phenylephrine (see Table 1). The prolonged mydriasis limits the usefulness of this drug as a diagnostic aid. After topical administration, chemosis can be observed in the dog [65] and salivation may be seen in the cat [62]. Psychotic behavior has been reported in human beings administered cyclopentolate 2% topically [88].

Adrenergic agents (sympathomimetics)

Adrenergic agents, or sympathomimetics, exert their effects by directly binding α- or β-adrenergic receptors or by indirectly increasing activity of NE at the neuroeffector junction. The α-adrenergic receptor agonists epinephrine, dipivefrin, and phenylephrine are mydriatic agents with minimal cycloplegic activity and cause vasoconstriction and reduction of IOP. These agents are employed as diagnostic tools, surgical adjuncts, and in the treatment of glaucoma. The α_2-adrenergic agonists apraclonidine and brimonidine and the β-adrenergic antagonists lower IOP and are used in the treatment of glaucoma.

Adrenergic receptor agonists

Epinephrine is an α- and β-adrenergic agonist. Epinephrine is available as hydrochloride or borate salts in 0.5% to 2% topical solutions and as a 1% solution in combination with pilocarpine (see Table 1). Epinephrine 2% produces mydriasis and reduction of IOP in normal and glaucomatous Beagles [89]. Topical administration of 0.1% or 2% solution does not result in mydriasis in the dog or cat, respectively (see Tables 2 and 3) [62,65]. Epinephrine is used for intracameral injection of 0.1 to 0.2 mL at a dilution of 1:10,000 for cataract surgery, hemostasis of intraocular hemorrhage, and short-term pupillary dilation [90]. Alternatively, an intraocular irrigation solution can be created by adding 1:1000 epinephrine, 1 mL, per 500 mL of irrigation fluid for intraoperative use [81]. A sterile preservative-free preparation should be selected for intraocular use, because corneal edema can develop if epinephrine solutions containing the antioxidant sodium bisulfite are used [91]. Side effects as a result of systemic absorption include hypertension, tachycardia, and arrhythmias. Administration during halothane anesthesia can cause ventricular arrhythmias and ventricular fibrillation [69,92].

Phenylephrine HCl is an α_1-adrenergic agonist with little effect on β-adrenergic receptors and is available in 2.5% and 10% solutions (see

Table 1). Phenylephrine 10% causes pupillary dilation in dogs for up to 18 hours (see Table 2) [65]. Used alone, phenylephrine does not cause mydriasis in cats, cattle, or horses; however, it can be used in combination with other mydriatics for enhanced dilation (see Tables 3–5) [62–64,93]. As α-adrenergic agonists, epinephrine and phenylephrine cause vasoconstriction and can be used to differentiate congestion of superficial conjunctival vasculature from that of deep episcleral vasculature. The former blanch with topical application, whereas the latter do not blanch or blanch incompletely [69]. In low concentrations (0.1%), topical phenylephrine or epinephrine may be used for symptomatic treatment of Horner's syndrome [69]. Phenylephrine should not be used in cases with corneal ulceration because it may cause corneal edema and endothelial toxicity [94]. Systemic absorption, particularly with repeated instillation of a 10% solution, may result in systemic hypertension or ventricular arrhythmia [95].

Phenylephrine may be used in the diagnosis and neuroanatomic localization of anisocoria caused by sympathetic denervation (ie, Horner's syndrome) [53,58]. The clinical signs of Horner's syndrome are miosis, ptosis (drooping of the upper lid), reverse ptosis (elevation of the lower lid in cats, primates, and dogs), enophthalmos, and elevation of the third eyelid. Pharmacologic testing with the indirect-acting sympathomimetics hydroxyamphetamine or cocaine and the direct-acting sympathomimetic phenylephrine should be performed 24 hours apart. Phenylephrine is applied to both eyes in a unilateral lesion, or to one eye in cases of bilateral miosis, at a concentration of 0.25% to 10% [6,52,53]. Upregulation of adrenergic receptors on denervated iris dilator muscle and hypersensitivity to dilute phenylephrine occur within a few days in lesions of the postganglionic sympathetic neuron [21]. Postganglionic neuron lesions typically respond with mydriasis, retraction of the third eyelid, and resolution of ptosis and enophthalmos within 5 to 8 minutes [6]. Central and preganglionic neuron lesions typically do not dilate or dilate more slowly (30–40 minutes) [53].

Dipivalyl epinephrine, or dipivefrin HCl, is a pivalic acid diester of epinephrine and is a prodrug of epinephrine. It is an α- and β-adrenergic agonist and is available as a 0.1% solution. After topical application, corneal esterases convert the compound to pivalic acid and the active agent epinephrine [96]. The benefits of this lipophilic prodrug formulation include increased corneal penetration (17 times that of epinephrine); thus, a lower concentration is required for equivalent therapeutic effect [97]. Unlike epinephrine, dipivefrin does not cause vasoconstriction of conjunctival vessels. Dipivefrin is a mydriatic and is as effective as epinephrine as an ocular hypotensive agent in the dog [89].

Apraclonidine HCl and brimonidine tartrate are α_2-adrenergic agonists and cause a decrease in aqueous humor flow rates [98]. Apraclonidine has been demonstrated to lower IOP in normal dogs and cats [99,100]. These agents are discussed in elsewhere in this issue.

Indirect-acting sympathomimetics

Hydroxyamphetamine and cocaine are indirect-acting sympathomimetic drugs that do not bind adrenergic receptors directly but act through various mechanisms to increase NE in the synaptic cleft. Both drugs are poor mydriatic agents in the dog (see Table 2), and their use in veterinary ophthalmology is limited to pharmacologic testing of Horner's syndrome. Use of either agent for testing of Horner's syndrome should be performed 24 hours before testing with the direct-acting sympathomimetic phenylephrine.

Hydroxyamphetamine stimulates release of stored NE from intact adrenergic nerve endings. This drug is currently available only as a 1% solution in combination with 0.25% tropicamide (Paremyd; see Table 1). Hydroxyamphetamine can be compounded, and concentrations of 1% to 5% may be used for pharmacologic localization of Horner's syndrome [101]. In a central or preganglionic neuron lesion, the postganglionic sympathetic neuron remains intact and hydroxyamphetamine stimulates release of stored NE to cause pupillary dilation. Lesions of the postganglionic neuron do not respond to the drug, because there are no stores of NE to be released; therefore, there is no mydriasis. Topical application of a single drop of a 1% solution resulted in no pupillary dilation in the normal canine eye in one study (see Table 2) [65]. Because the effects are unrelated to the phenomenon of denervation hypersensitivity, and thus are not dose-dependent, multiple drops of a 1% solution or use of a 5% solution may be necessary. Application of a sufficient amount of drug to both eyes to induce mydriasis in the control eye is necessary for accurate test interpretation [6].

Cocaine prevents NE reuptake by the adrenergic neuron at the presynaptic terminal, resulting in accumulation of NE at the neuroeffector junction [102]. Cocaine is a topical anesthetic and a weak mydriatic agent in human beings; however, it has little to no effect on the normal canine pupil (see Table 2) [65]. Topical application of one drop of a 4% to 6% cocaine solution has been reported for confirmation of Horner's syndrome in the dog and cat [6,69]. If sympathetic innervation to the iris dilator muscle is intact, cocaine prevents reuptake of NE, and the increase of NE at the neuroeffector junction results in mydriasis. A sympathetically denervated eye experiences no dilation or may display impaired dilation if the lesion is central, whereas the control eye dilates.

Adrenergic receptor antagonists

Dapiprazole HCl (Rev-Eyes; Bausch & Lomb, Rochester, NY) is an α-adrenergic antagonist, producing miosis through blockade of primarily α_1 receptors in the iris dilator muscle. The use of dapiprazole 0.5% for reversal of tropicamide 1%- and phenylephrine 2.5%-induced mydriasis in human beings has been reported [103]. The application of two drops of dapiprazole 0.5%, followed by two drops 5 minutes later, resulted in a premydriatic

pupil size in most eyes within 2 hours. Interestingly, dapiprazole, an adrenergic antagonist, was effective in reversing mydriasis caused by the muscarinic antagonist tropicamide. Side effects were limited to conjunctival hyperemia. There are no reports on the efficacy of this agent in companion animals.

There are a number of β-adrenergic antagonists commercially available for topical ophthalmic use. Betaxolol HCl and levobetaxolol are selective β_1 antagonists. Levobetaxolol is the S-isomer and more active enantiomer of betaxolol. Carteolol HCl, metipranolol HCl, levobunolol HCl, and timolol maleate are nonselective β_1 and β_2 inhibitors. These drugs are commonly employed in the treatment of glaucoma as IOP lowering agents, and the reader is directed elsewhere in this issue for further discussion.

Summary

The parasympathetic and sympathetic divisions of the autonomic nervous system are involved in homeostatic control of a wide variety of ocular functions, including accommodation, pupillomotor control, lacrimation, eyelid position, and aqueous humor production. Familiarity with the functional anatomy of the autonomic nervous system is paramount to the understanding and application of the large number of autonomic drugs used in veterinary ophthalmology. The cholinergic and adrenergic agents discussed in this article are commonly employed to facilitate routine ophthalmic examination, in the diagnosis of autonomic dysfunction, and in the treatment of a variety of ocular diseases.

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