Ocular Autonomic Nervous System

Subjects: Ophthalmology

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The autonomic nervous system (ANS) confers neural control of the entire body, mainly through the sympathetic and parasympathetic nerves. Several studies have observed that the physiological functions of the eye (pupil size, lens accommodation, ocular circulation, and intraocular pressure regulation) are precisely regulated by the ANS. Almost all parts of the eye have autonomic innervation for the regulation of local homeostasis through synergy and antagonism. With the advent of new research methods, novel anatomical characteristics and numerous physiological processes have been elucidated.

autonomic nervous system | eye | anatomy | pupil light reflex | choroidal blood flow | aqueous humor

1. Autonomic Control of the Eye

1.1. Cornea

The cornea is one of the most densely innervated parts of the human body with a rich supply of sensory and autonomic nerve fibers [1]. Sensory nerves, mainly originating from the ophthalmic branch of the trigeminal nerve, comprise the majority of the nerves in the cornea. Sympathetic nerves originating from the SCG are found in the corneas of mammals, and their densities vary in different species. Parasympathetic innervation originating from the CG has been also reported in cats and rats [2][3][4].

The corneal innervation was first described in detail in 1951 [5], but the description of human corneal nerves was relatively limited at that time. Recent studies have suggested that nerve bundles enter the peripheral cornea radially and parallel to the corneal surface; thereupon, they lose their perineurium and myelin sheaths at approximately 1 mm from the limbus and about 0.1 nm from the ocular surface. These nerve bundles radiate through the middle third of the corneal stroma and further subdivide to form smaller branches that comprise a moderately dense midstromal plexus and a dense subepithelial plexus (SEP) before finally passing through the anterior elastic layer and entering the corneal epithelium [3][6][7].

These sensory and autonomic nerves also play a key role in maintaining the optimal health of the ocular surface. Corneal nerves can release soluble trophic substances that promote lacrimal gland secretion, induce blinking reflexes, and maintain the integrity of the ocular surface [8]. Substance P (SP) exerts a strong synergistic effect with insulin-like growth factor-1 (IGF-1) or epidermal growth factor to promote corneal epithelial migration, adhesion, and wound closure. Several other neuropeptides also play important roles in the cornea (**Table 1**) [9][10][11].

Table 1. Various peptide and transmitters in the cornea of mammals.

Compound.	Mechanism
Substance P	Epithelial renewal and wound repair
CGRP	Epithelial renewal and wound repair
Norepinephrine	Epithelial renewal and wound repair; stimulate proliferation and migration of corneal epithelial cells
Acetylcholine	Promote DNA synthesis in epithelial cells
VIP	Protect corneal endothelial cells from oxidative stress
Neurotensin	Increases keratocyte proliferation; decreases keratocycte apoptosis
Nerve growth factor	Sustain homeostasis and regeneration of epithelium and stroma

1.2. Iris

The iris is a circular pigmented membrane located in front of the lens, it divides the cavity between the cornea and lens into an anterior chamber and a posterior chamber.

The iris controls the amount of light entering the eye by adjusting the pupil. The preganglionic parasympathetic axons originating from the EWpg innervate the pupillary sphincter through the short ciliary nerve. These axons act on the muscarinic receptors of the pupillary sphincter, and mediate pupillary constriction. Sympathetic innervation originates from the SCG and provides a reciprocal function via the long ciliary nerves which control pupil dilation [12][13]. The ophthalmic nerve, a branch of the trigeminal nerve, is also involved in the innervation of the iris [14]. Previous studies have suggested that the trigeminal nerve offers sensory transduction and induces substance P-related contractions for mediating protective reflexes [15]. However, recent studies have demonstrated that the trigeminal nerve also affects smooth muscle response, intraocular blood vessels, and immune function by releasing various peptides [12]. Based on these anatomical functions and innervations, pupil evaluation can be a simple and convenient method to detect autonomic disorders and may therefore have potential diagnostic value [16].

The iris of several vertebrate species has rhodopsin, a molecule that enables photomechanical responses (PMR). Rhodopsin enables pupillary constriction in response to light without the need for a central nervous reflex. This process may involve (1) rhodopsin-activated G-protein, (2) phospholipase C, (3) inositol triphosphate, or (4) Ca^{2+} [17][18]. Moreover, PMR can be inhibited by β-adrenergic agonists, but not by α-adrenergic agonists [18][19]. After the application of β-adrenergic agonist to toad sphincter cells, the availability of Ca^{2+} ions for sphincter contraction was found to be altered, followed by pupillary dilation [19]. Generally, the sympathetic and parasympathetic systems work antagonistically to control the contraction and relaxation of the iris muscles. The ratio of innervations from these systems differs among species [12].

1.3. Anterior Chamber Angle

The main outflow pathway of aqueous humor (AH) comprises the trabecular meshwork (TM), the endothelial lining of Schlemm's canal, juxtacanalicular connective tissue, collecting channels, and aqueous veins. Additionally, the outflow resistance of the TM pathway seems to be regulated by the contraction of the scleral spur (SS) cells and ciliary muscles [20]. In almost all species, the SS cells contain SP-positive axons, most of which also immunostain for CGRP [14][21]. In humans, the axons in the TM and SS show immunoreactivity (IR) to SP, CGRP, NPY, VIP, and NOS, while in monkeys, sympathetic SS cell innervations are more frequently observed [22][23][24][25][26]. These cholinergic and nitrergic nerve terminals may induce the contraction and relaxation of TM and SS cells [27]. However, research on human and monkey eyes has shown few TH-positive and VIP-positive nerve fibers, as well as the absence of NPY-positive fibers in SS and TM [27]. Only a small amount of opioid peptidergic innervation has been reported in the anterior eye segment of the eye in rats. SP, CGRP, NPY, and VIP immunoreactivity also occurs in the ciliary process, ciliary muscles, and ciliary blood vessels [28]. A recent study demonstrated the presence of efferent nerve pathways from the hypothalamus to the autonomic innervation in the bilateral anterior chamber [29]. When inflammation occurs, peptide expression in the bilateral anterior chamber is upregulated [30]. The immunolabeling pattern for TM is similar in humans and pigs [31].

Nomura found that approximately one-third of the innervation in the TM is sympathetic in monkeys, and that two-thirds are parasympathetic [32]. In human TM and cultured TM cells, most receptors on the sympathetic nerves appear to be the β2 adrenergic subtype [33][34].

1.4. Lacrimal Glands

The lacrimal gland is located in the orbit of the human eye. Lacrimal secretions are vital to the health and maintenance of the cells on the ocular surface (conjunctiva, corneal epithelium). Regulation of lacrimal gland secretion involves the following: (1) stimulation of the sensory nerve on the ocular surface and (2) parasympathetic and sympathetic activation of the lacrimal secretory cells [35]. Mechanonociceptors, polymodal nociceptors, and cold receptor fibers are distributed on the conjunctiva and cornea [36][37]. Stimulation of the corneal polymodal nociceptors causes reflex tear secretion, while mechanonociceptors and cold receptors are less effective in mediating this effect. Interestingly, tear secretion does not increase with increased stimulation of the conjunctival receptors [38].

Tear production is regulated by both the sympathetic and parasympathetic nerves. Generally, sympathetic nerves affect tear secretion via the following two methods: (1) alteration of blood flow [39] and (2) via increased secretion of sympathetic neurotransmitters [40][41]. However, the role of sympathetic nerves in the lacrimal gland remains uncertain. Some studies have suggested that electrostimulation of the SCG alters tear secretion, while other studies report contradictory findings [42][43][44]. The content of the tear secretion remains unaltered even after SCG ablation, indicating that tear secretion is not related to sympathetic postganglionic nerves [45]. Tear secretion is mainly controlled by the parasympathetic nerves [45]. These nerves mediate tear secretion by releasing Ach and

activating the M3 muscarinic Ach receptors [46][47]. Moreover, marked reduction in lacrimal gland secretion can be observed in rabbits with parasympathetic nerve lesions [48].

1.5. Retina

The neural retina is a layered structure that converts photic illumination into visual information and then transmits this signal to the brain. The retinal circulation and the choroidal circulation, both of which originate from the ophthalmic artery, are responsible for supplying oxygen and nutrition to the retina. Retinal circulation provides a low level of blood flow and a high level of oxygen extraction, contrary to that in choroidal circulation [49][50]. There is limited insufficient evidence of autonomic innervation in the intraocular branch of the central retinal artery (CRA) [51][52]. Instead, retinal circulation is generally considered to be autoregulated by local mechanical and chemical stimulations based on the sensation of the oxygen levels [53][54].

The preocular CRA in humans receives adrenergic and cholinergic nerve fibers, suggesting sympathetic and parasympathetic innervation. However, SP, CGRP, and VIP were not detected in the nerve fibers, indicating a lack of peptidergic innervation [55]. Similarly, immunohistochemical and histochemical studies have confirmed the presence of [48] parasympathetic nerve (NOS/VIP/NADPH-d), sympathetic nerve (TH), and CGRP-positive afferent nerve fibers in the vicinity of the monkey and rat CRA [56][57]. Substance P-positive nerve fibers have also been identified around the CRA in rabbits [58]. Early research on several monkey species has shown that adrenergic innervation is only present posterior to the lamina cribosa in the intraorbital part of the optic nerve [52][59]. Postganglionic nerves of the pterygopalatine ganglion release NO, causing vasodilation of the arterial smooth muscles [60][61]. The sympathetic innervation gradually decreases with increasing age [62], which may lead to significant loss of photoreceptor cells and increased reactivity of the glial cells [63].

1.6. Choroid

The choroid makes up the posterior part of the uvea, located between the retina and sclera, and is mainly composed of blood vessels. Neurons in the choroid, which mainly regulate choroidal circulation, are also called choroidal ganglion cells or intrinsic choroidal neurons (ICN) [64][65]. There are approximately 2000 ICNs in each eye. Most of these ICNs are clustered in the temporal and central regions of the submacular area. In contrast, these neurons are largely accumulated at the periphery in rabbits, possibly because rabbits lack the macula [66]. In other species, there are only approximately 500 ICNs, with largely uniform distribution. In different avian species, the number of ICNs varies from less than 500 in quail to more than 6000 in geese. These cells are mainly concentrated at the temporocranial area in Galliformes, while in Anseriformes, they form a belt that extends in the cranionasal to temporocaudal direction [67].

In mammals, the primary input of the parasympathetic nerves originates from the PPG via the facial nerve [68][69]. Although some physiological changes have been noted upon stimulation of the CG, the innervation of the choroid in mammals has not been confirmed to date [70][71][72]. However, in avian, the CG supplies most of the parasympathetic innervation [73], these parasympathetic input increases choroidal blood flow of via vasodilation. On immunohistochemistry, almost all ICGs are stained for nNOS and VIP, half of the cells show immunoreactivity for

calretinin, while the individual cells are stained only for just neuropeptide Y (NPY) [74][64]. The choroid contains large amounts of TH(+) and NPY(+) ICNs in the central temporal area [75]. Using immunohistochemistry method, sympathetic innervation was observed derived from the SCG and modulates the NO/VIP/GAL innervation of vascular and non-vascular smooth muscle provided by ICN [76][77]. Such dual innervation balances the increase and decrease in choroid blood flow. Despite aging, the choroidal innervation patterns and neural transmitters remain unaltered to some extent [64]; however, some studies have suggested a decrease in adrenergic fibers and VIP(+) nerve fibers [78][79][80]. SP (+) and CGRP (+) ICNs have been identified in choroidal whole mounts, suggesting choroidal innervation by sensory nerves. Additionally, these ICNs were found to be more concentrated in the temporal and central regions and are thought to be involved in mediating blood flow and vascular architecture [81].

2. Physiological Effect

2.1. Pupil Adjustment

The size of the pupil varies with the intensity of incident ambient light, which forms the PLR. Generally, pupil dilation and constriction depends on both autonomic innervation and local reflexes [82]. Light incident into one eye can cause constriction of both the eyes, including the unstimulated eye. These phenomena are termed direct and consensual responses. In early studies, the consensual response was thought to be limited to “higher” mammals. However, recent studies have provided more evidence to support that consensual response also occurs in “lower” mammals, and even non-mammals; although, in non-mammalian species, consensual PLR is indistinctive [83][84].

2.2. Ocular Blood Flow

There are no blood vessels in the normal cornea, while the limbus contains abundant blood vessels that supply nutrients and oxygen. Similar to the cornea, the scleral stromal layer has no blood vessels, except those passing through. However, the sclera surface and optic nerve lamina cribrosa are rich in blood vessels and form a vascular network. These arteries are derived from the ophthalmic artery, which is the only artery supplying the eye. This blood vessel receives autonomic innervation and mainly supplies the uvea and retina. Hence, nearly all ocular circulation is modulated by autonomic nerves, except the retinal blood vessels [53].

The choroidal circulatory system is responsible for supplying the photoreceptors and the retinal pigment epithelium. Reduced blood flow can cause a rapid loss of photoreceptor cells [85]. Generally, autonomic innervation of the choroid includes parasympathetic pathways that dilate vessels and increase blood flow, sympathetic pathways that constrict vessels and decrease blood flow, and the local trigeminal system that transfers sensory input, or directly releases SP/CGRP in response to activating stimuli [86].

The SSN–PPG circuit mediates choroidal parasympathetic vasodilation, which seems to contribute to ChBF pressure regulation in case of low arterial blood pressure (ABP) [87][68]. In mammals, the PPG receives parasympathetic input from the SSN [88], and its preganglionic root, which contains NOS, VIP, and ChAT, directly

projects to the choroid [89]. Many studies have discussed the role of VIP, NO, and ACh in mediating ChBF after stimulation of the facial nerve or SSN. Intravenous injection of VIP leads to increased intraocular pressure (IOP) and ChBF [90]. Different vasoactive substances affect the excitation frequencies of different nerves. In rabbits, the formation of NO (endothelial or neurogenic) is involved in uveal vasodilation caused by low-frequency facial nerve stimulation, while at high frequencies, other neurotransmitters also seem to be involved [91]. ChBF was significantly increased following facial nerve stimulation in monkeys, cats, and rabbits. Moreover, VIP was suggested as the peripheral molecule causing the vasodilation [92].

Based on immunohistochemical experiments in pigeons, the PPG seem to be composed of three to four main sub-ganglia connected to each other. Each main nerve contains 50–200 neurons, as well as several small ganglia. These neurons in birds release VIP and NO, and possibly Ach [93]. In mammals, the regulatory effect of PPG on ChBF appears to be similar as that in birds and can partially compensate for the decreased ABP. This may be a common ocular mechanism in warm-blooded vertebrates [94]. The avian choroid has a distinctive parasympathetic input of the CG and occupies a dominant position [86]. Using anatomical knowledge and electrical stimulation experiments, the central components from circuits in avian ChBF regulation were identified as follows: the retina–contralateral SCN that contains SP (+) neurons–medial EW (EWm), which controls ChBF via its ipsilateral projection to choroidal neurons of the CG [95]. Cantwell and Cassone indicated that SCN in avians can be divided into medial SCN (mSCN) and visual SCN (vSCN), while the latter is considered to participate in ChBF regulation [96][97]. If SCN was activated by retinal illumination of the contralateral eye, the choroidal volume appeared to increase (vasodilation) corresponding to a similar increase in systemic blood pressure [98]. This complex parasympathetic reflex response might be adaptive and is involved in maintaining the health of photoreceptor cells [99]. Cholinergic fibers of the CG are widely distributed in the choroid of avians. M2, M3, and M4 type receptors have been found in the retina, retinal pigment epithelium, choroid, and ciliary body [100]. After specifically suppressing these muscarinic receptors, M3 muscarinic receptors were observed to dominantly facilitate the EW-mediated increase in ChBF, with endothelial cell stimulation to release NO [101].

In both mammals and birds, the sympathetic nerves innervating the choroid are derived from noradrenergic nerve fibers of the cervical ganglia [86]. Stimulating the unilateral sympathetic nerve causes a large reduction in the ChBF [102][103]. After ICN transection, the choroids demonstrate increased vascularity and sympathetic denervation of the choroid and retinal defects [104][105]. These effects may be mediated by adrenoceptors. Previous research suggested that α-and β-adrenergic blocks can cause choroidal vasodilation and vasoconstriction, respectively, in rabbits [106]. This result is consistent with the observation that venous NPY treatment significantly reduces ChBF [107]. The trigeminal nerve branches that contain SP and CGRP innervate the choroid in mammals and birds [28]. Trigeminal nerve stimulation leads to the local release of vasodilators, SP, and CGRP [108]. Some researchers have recognized that the TG may be involved in the temperature-dependent regulation of ChBF. However, the specific underlying mechanisms need to be further investigated [86].

2.3. Intraocular Pressure Regulation

Aqueous humor (AH) is a transparent fluid found in the anterior and posterior chambers. It is mainly responsible for nutrient delivery and IOP regulation. It is produced by the ciliary epithelium and exits the eye through two independent outflow pathways, which involves the trabecular meshwork (TM) and unconventional pathway (uveoscleral). Recent evidence has suggested that another unconventional pathway (uveolymphatic route) has potential for maintaining IOP [109].

2.4. Lens Accommodation

The accommodation reflex, also referred as near reflex, is the response for focusing on near objects [110]. The afferent limb of this reflex is through the optic nerve and efferent limb was considered to be the EWpg, EWcp, and the oculomotor [111]. The final effects of this reflex consists the convergence of both eyes and contraction of the ciliary muscle leading to the change of lens accommodation and pupillary constriction [112]. The ciliary muscle of mammals, and its homologues in fish and amphibia are contracted via cholinergic muscarinic mechanisms, while in birds and reptiles, acetylcholine acts via nicotinic receptors [12].

Recent research on primates suggested that the premotor neurons controlling the lens of unilateral eye are distributed in the bilateral midbrain. By retrograde tracing methods, some of the premotor neurons in the supraoculomotor area and central mesencephalic formation were doubly labeled, while others were labeled from either the ipsilateral or contralateral eye, which suggest the both monocular control and binocular control of lens accommodation [113].

Because of all the recent and past work that has been performed, lens accommodation to vergence angle and other aspects of eye movements are connected [113][114][115][116]. A cohort study showed that with lens accommodation, anterior chamber depth, and anterior chamber angle remained stable while the pupil diameter varied [117].

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