Autonomic Nerve Dysfunction in Ocular Diseases

AKIRA MURAKAMI*

*Department of Ophthalmology, Juntendo University Graduate School of Medicine, Tokyo, Japan

The autonomic nervous system influences numerous ocular functions and disorders. It is well known that various pupillary abnormalities and ptosis are caused by local dysfunction of the autonomic nervous system. Furthermore, ocular symptoms can occur as a manifestation of systemic autonomic dysfunction. Understanding the pathophysiology of the autonomic nervous system is useful for management of patients with various eye diseases.

Key words: autonomic nervous system, dry eye disease, glaucoma, central serous chorioretinopathy

Introduction

The autonomic nervous system has an important influence on ocular function and ocular disorders. The levator palpebrae superioris (Müller’s muscle) is innervated by sympathetic fibers, and mild ptosis is one of the features of Horner’s syndrome. Various pupillary abnormalities can occur due to autonomic dysfunction, such as miosis in Horner’s syndrome and dilated myotonic pupils in Adie syndrome. The ciliary muscle, which contracts to alter the shape of the crystalline lens for accommodation, is innervated by parasympathetic nerves, so blurred vision can be caused by cycloplegia in patients taking anticholinergic medications. The lacrimal gland (LG) is also under parasympathetic control, and its secretions make a large contribution to the aqueous component of the tear film. Conjunctival goblet cells, which contribute to the mucous layer of the tear film, are under parasympathetic control as well. Moreover, the autonomic nervous system innervates the ocular blood vessels. Finally, it is generally accepted that systemic or local dysfunction of the autonomic nervous system is a causative factor in some diseases of the retina and the optic nerve. This review discusses autonomic regulation of the ocular surface and ocular vascular system, as well as the role of the autonomic system in various diseases.

Autonomic regulation of the ocular surface

The ocular surface is bordered by the upper and lower eyelids and it consists of two major territories, which are the cornea and the conjunctiva. Unlike the skin of the body, the ocular surface is covered by a thin tear film. The LG makes the main contribution to the aqueous component of the tear film, while conjunctival goblet cells provide the mucous component of the tear film. The meibomian glands are involved in synthesis and secretion of lipids that promote tear film stability and prevent its evaporation. Parasympathetic innervation of the LG and conjunctival goblet cells is mediated via the pterygopalatine ganglion (PPG). The tear production reflex involves motor neurons within...
the superior salivatory nucleus (SSN), which send projections to parasympathetic cholinergic motor neurons in the PPG that innervate the lacrimal gland and promote tear production by stimulation of the glandular acini. Several studies have demonstrated that loss of parasympathetic function results in reduced tear flow in humans. Meibomian glands are innervated by sensory, sympathetic and parasympathetic nerves, but the exact functions of these nerves are not well understood.

Dry eye disease (DED) is a common condition that causes ocular discomfort and visual disturbance, which can have a substantial effect on the quality of life. It has a multifactorial etiology that includes tear film instability, increased tear film osmolality, and inflammation with potential damage of the ocular surface. Aqueous tear-deficient dry eyes is an isolated idiopathic condition that occurs in postmenopausal women. However, it is also frequently associated with Sjögren syndrome (SS), rheumatoid arthritis (RA), or systemic lupus erythematosus (SLE). It has long been believed that autoimmune destruction of the exocrine glands leads to hypofunction and dry eye symptoms in patients with SS. However, there are several lines of evidence for a different pathophysiology, and some researchers have suggested that dysfunction of the autonomic nervous system might modulate exocrine gland function. A similar hypothesis has also been proposed for the pathogenesis of dry eye symptoms in patients with systemic neurodegenerative diseases. It is well known that Parkinson disease (PD) is associated with an increased risk of dry eyes. Although various abnormalities of tear film production can occur in PD patients, some researchers have hypothesized that tear film impairment may be the result of autonomic dysfunction due to presence of Lewy bodies in the sympathetic ganglia, substantia nigra, and peripheral parasympathetic ganglia. The cornea receives innervation from the ophthalmic branch of the trigeminal nerve and corneal nerves have an important neurotrophic role in maintaining the integrity of the cornea. Small unmyelinated nerve fibers enter the cornea from its periphery and run through the corneal stroma before penetrating the subepithelial Bowman’s membrane to form the sub-basal nerve plexus. Recently, in vivo confocal microscopy (IVCM) has allowed noninvasive imaging of nerves in the living human cornea. Studies using this technique have demonstrated that changes of sub-basal corneal nerves occur in patients with peripheral neuropa-thies such as diabetic neuropathy. IVCM has also been used to evaluate the ocular effects of neurodegenerative conditions and autoimmune diseases. These studies might help to elucidate the underlying role of autonomic dysfunction in the different subtypes of DED.

Ocular circulation and its role in disease

The eye has two separate vascular systems, which are the retinal and uveal vessels. The retinal system supplies the inner retina, while the uveal system supplies the outer retina including the photoreceptors, as well as supplying the retinal pigment epithelium. Retinal vessels have little, if any, autonomic innervation, but demonstrate robust auto-regulation. The uveal vessels supply about 85% of total retinal blood flow. In general, parasympathetic innervation of these vessels seems to ensure continued perfusion of ocular tissues despite a decrease of mean arterial pressure resulting from blood loss or other causes of systemic hypotension, while sympathetic innervation appears to prevent...
excess perfusion of ocular tissues due to an increase of mean arterial pressure resulting from exercise or other causes of systemic hypertension. It has been proposed that dysregulation of the choroidal circulation may lead to various retinal diseases and optic neuropathy, including age-related macular degeneration, central serous chorioretinopathy (CSCR), and glaucomatous optic neuropathy.

In CSCR, macular detachment is caused by accumulation of serous fluid at the posterior pole, which results in a circumscribed area of retinal detachment (Figure-2). The cause of CSCR is largely unknown, and it is classified as idiopathic. A possible role of psychological stress as a factor contributing to the development of CSCR has been suggested, and it is also known to be associated with type A behavior and pregnancy. While it is generally accepted that patients with CSCR have bilateral diffuse choroidal dysfunction, the disease is often active in only one eye. Many risk factors for CSCR have been identified, but the most consistent is exposure to corticosteroids due to therapeutic administration or endogenous overproduction such as in Cushing syndrome. In a case–control study, CSCR patients showed a significant decrease of parasympathetic activity and a significant increase of sympathetic activity. A review also found that patients with CSCR have significantly decreased parasympathetic reactivity and sympathomimetic medication. It is generally thought that CSCR arises from a systemic event that may affect the choroidal vasculature, which is under autonomic regulation.

Bousquest et al. reported that shift work is an independent risk factor for CSCR. Recently, melanopsin was found as a photosensitive pigment in a subset of retinal ganglion cells directly sensitive to light. These intrinsically photosensitive retinal ganglion cells play a critical role in nonvisual, non-image-forming responses to light, such as the pupillary light reflex and circadian photo-entrainment. Photic regulation of production of melatonin by the pineal gland is exclusively sympathetic.

Melatonin production is suppressed through activation of melanopsin ganglion cells in the retina during daylight, explaining the reduced level of melatonin in shift workers who are exposed to light during the nighttime. It is interesting that a small study has demonstrated a potential benefit of oral melatonin in patients with chronic CSCR.

Glaucoma is a group of progressive optic neuropathies characterized by degeneration of retinal ganglion cells and resultant changes of the optic nerve head. Although the pathogenesis of glaucomatous optic neuropathy is not fully understood, elevation of the intraocular pressure (IOP) is related to death of retinal ganglion cells. The balance between secretion of aqueous humor by the ciliary body and its drainage through two independent pathways – the trabecular meshwork and uveoscleral outflow – determines the intraocular pressure. Glaucoma can be classified into 2 broad categories, which are open-angle glaucoma and angle-closure glaucoma. In Japan, more than 90% of patients have open-angle glaucoma, but angle-closure glaucoma is disproportionately responsible for severe loss of vision. Both open-angle glaucoma and angle-closure glaucoma can be primary diseases, while secondary glaucoma can result from trauma, certain medications such as corticosteroids, inflammation, and pseudo-exfoliation. Population–based studies have shown that glaucoma is also common among people with an IOP in the statistically normal range and this is called normal tension glaucoma (NTG). Asians appear to be especially susceptible to NTG, with the Japanese Tajimi study showing that the prevalence of primary open angle glaucoma (POAG) was 3.9%, with 92% of affected patients having an IOP ≤21 mmHg. The pathogenesis of NTG remains unclear and it is thought that interactions among various systemic factors are involved in the onset.
and progression of this disease. Several population-based studies have suggested that reduced diastolic ocular perfusion pressure is a risk factor for the development of optic neuropathy. Orthostatic hypotension, autonomic dysfunction, peripheral microcirculatory abnormalities, and primary vascular dysregulation are characteristic findings in glaucoma patients. Other observations suggestive of vascular and perfusion abnormalities include an increased prevalence of systemic conditions such as obstructive sleep apnea (OSA) and Raynaud’s phenomenon in patients with NTG.

Conclusions

As described above, autonomic dysfunction seems to be a causative factor in various ocular diseases, but we still know very little about managing and correcting ocular autonomic dysfunction. Accordingly, more research is needed on the neural control of ocular function and the role of autonomic regulation in normal visual processes.

References