IMPLICATIONS OF NERVE CONTROL OF CHOROIDAL BLOOD FLOW IN OCULAR DISEASES

IMPLICACIONES DEL CONTROL NERVIOSO DEL FLUJO SANGUÍNEO COROIDEO EN LAS ENFERMEDADES OCULARES

DE HOZ MONTAÑANA R1, RAMÍREZ SEBASTIÁN AI1

Physiologically, one of the main functions of the choroids is to nourish (supply O₂ and glucose) the outermost layers of the retina (mainly photoreceptors and RPE). However, the choroids seem to be perfused in a proportion which exceeds its supply needs, suggesting therefore an additional role explaining the high rate of choroidal flow. It is believed that this flow could aid in maintaining IOP as well as carry out a thermal regulation action through the following mechanisms: dissipating the heat generated during the visual phototransduction process, preventing overheating of the external retina during exposure to bright light and finally warming the intra-ocular structures which may lose heat while exposed to extreme environmental conditions.

In recent years it has been evidenced that nerve control plays an important function in regulating said choroidal blood flow.

The neuroregulation of the uveal flow is governed by multiple mechanisms. This regulation would be carried out directly through peri-vascular innervation, which would allow a balance between vessel constriction and dilatation necessary for maintaining blood flow, whereas the indirect regulation would be carried out through paravascular fibers, both through typical neurotransmitters and by neuropeptides released by sympathetic, parasympathetic and sensory terminations of the stroma, and diffusible factors such as nitric oxide.

It has been observed that in the human choroids, both the perivascular and paravascular fibers are marked with antibodies against sympathetic system neuropeptides (Neuropeptide Y [NPY], Parasympathetic (Vasoactive Intestinal Peptide [VIP]) and Sensitive (Substance P [SP] and Calcitonine Gene Related Peptide [CGRP]).

Sympathetic stimulation causes a sharp choroidal vasoconstriction and a fall in IOP due to a reduction in the ocular blood volume (choroidal flow reductions of up to 60%). This response is mainly executed by the stimulation of α-adrenergic receptors located in the smooth muscle cells of the vessels. Sympathetic innervation causes the choroids to be under a vasoconstrictor tone, which suggests that this could protect the retina and the optic nerve head from hyper perfusion and rupture of ocular barriers (which could occur in certain circumstances such as high arterial pressure).

The role of parasympathetic innervation is not so well defined as the role of the sympathetic system. However, it has been observed that the choroids respond to parasympathetic collinergic stimuli (arriving through the short ciliar nerves) by means of vasodilatation. This vasodilatation would explain the light-induced reflex increase of choroidal flow.

Recently it has been proposed that the sensitive peripheral nerves also play an important role in regulating choroidal flow. Thus, the SP could have a visceral/motor function regulating choroidal flow during ocular irritation. Likewise, the CGRP has also been attributed a vasodilatation role as a collinergic co-mediator together with SP.

In the light of the importance of nerve control in regulating choroidal blood flow, it follows that damages in the choroidal innervation could be involved in the vascular alterations which occur in some eye diseases. Experimental research has proved that sympathetic innervation is critical for the regulation of choroidal vascularization and that the

1 Professor E.U. Institute of Ophthalmological Research Ramón Castroviejo. UCM. E-mail: rdehoz@med.ucm.es / airamirez@med.ucm.es
chronic loss of sympathetic activity may contribute to the abnormal vascular proliferation observed in diseases such as Age-Related Macular Degeneration (ARMD) and diabetic retinopathy. In addition, the loss of this innervation can lead to retinal edema, which could be an important development in diseases such as diabetes or high blood pressure where autonomous control is altered.

Axon damage in the Sympathetic Nervous System is a noteworthy event in diabetic retinopathy. In addition, the existence of a dysfunction of ocular sympathetic nerves has been suggested in diabetic patients, postulating that hyperglucemia events could determine increases in the choroidal flow and in the pressure of sub-macular choroid vessels as well as changes in the retina pigmented epithelium. Thus, the extravasation of fluid from the sub-macular choroidal vessels would be aggravated. The excess of intra-retinal liquid which originates diabetic macular edema would proceed not only from retinal vessels but also from the chorioids, reaching the retina through pigmentary epithelium lesions near to the involved choriocapillary.

The choroidal nerve fibers are more numerous in the center of the chorioids than in the periphery. This is even more notable in the sub-macular region where the axons form a delicate mesh in which we also find the highest percentage of NPY(+) and TH(+) choroidal ganglionary cells. The distribution of these cells (mostly in the sub-macular region) suggests the possibility that the vascular pathologies of certain ocular diseases, such as the diabetic macular edema or ARMD, are related to a possible dysfunction of these cells (2).

In ARMD the hemodynamic abnormalities have been described both as causal agents and as part of the pathological process. Using Doppler laser flowmetry it has been observed that the choroidal blood flow reduces with age and is lower in the non-exudative stages of macular degeneration than in controls. This effect is due to a reduction in blood flow volume (3). More longitudinal studies would be required to determine whether these alterations in the choroidal blood flow participate in some way in the development of choroidal neovascularization, and whether the flow measurements could identify ARMD subjects at risk of developing choroidal neovascularization. Similarly, it would be necessary to achieve a greater understanding of the possible involvement of the choroidal innervation and particularly of the sub-macular neurons in this eye disease.

Recently it has been postulated that the sensitive nerves could be involved in the regulation of the choroidal flow in a variety of inflammatory mechanisms which are involved in plasmatic vasodilatation and renewal. Their role has also been identified in vessel maintenance and renewal processes, with substantial involvement in the visual function (4). Thus, it has been suggested that changes in the choroidal thickness would play a main role in regulating the ocular refractive state, particularly in the recovery from myopy (5).

Accordingly, we must consider that sensitive as well as sympathetic peripheral innervation may have a large and significant role in regulating the choroidal vascular architecture. Moreover, considering the particular susceptibility to damage exhibited by peripheral innervation under a broad range of conditions including age, high arterial pressure, ocular hypertension and diabetes, the dysfunction of sympathetic and sensitive choroidal nerves could play a part in the etiology of eye diseases which appear to be associated to said conditions.

REFERENCES