EDITORIAL OPEN ACCESS

Neurovascular protection instead of only neuroprotection

Toshiyuki Oshitari

The maintenance of the normal functioning of neurons in the retina depends not only on neuron-to-neuron interactions but also on interactions of the neurons with vascular cells (pericytes and endothelial cells) and glial cells (Müller cells, astrocytes, microglia). This functional group of neuronal, vascular, and glial cells is called neurovascular unit (NVU). The NVU regulates the integrity of the blood-retinal barrier and the flow of blood in the vascular system. In the eyes, the majority of retinal and optic nerve disorders, such as diabetic retinopathy, age-related macular degeneration, retinitis pigmentosa, glaucoma, and neuromyelitisoptica (NMO), are due to dysfunctions of NVUs in the retina and optic nerve. Untreated, the dysfunctions of the NVUs will lead to neuronal death resulting in irreversible loss of vision.

Neuroprotective methods are generally designed to prevent injured neurons to progress beyond the point of irreversible changes. Considering the interactions of the components of the NVUs, the question arises on whether neuroprotection alone is sufficient for protecting retinal neurons in "neurovascular" retinal diseases.

As best of my knowledge, there has not been a large scale clinical trial that examined whether neuroprotective methods are effective in treating retinal and optic nerve disorders. This is probably because most neuroprotection target only neurons, and the glial and vascular cells are generally ignored. For example, ischemia can damage not only neurons but also glial and vascular cells. And yet, treatments for ischemia target only the neurons. However, investigators have begun to pay more attention to intercellular signaling and cell-matrix signaling as important elements to consider when neuroprotective agents and procedures are being developed.

A neurovascular niche is the site of micro interactions between neurons, vascular cells, and glial cells. After neuronal injury, regenerative and angiogenic processes begin with interactions between the neuronal precursor cells and vascular endothelial progenitor cells. This is reasonable because even if neoplastic cells are progenitor cells, differentiation of two kinds of progenitor cells should be more effective for the remodeling the neuronal system than only one kind of progenitor cell. That is why the entire NVU must be targeted for neuroprotection of the neurons in retinal and optic nerve diseases.

There are many potential mediators that can act on the altered NVUs in neurovascular diseases. However, most mediators have contradictory effects, i.e., those that exacerbate the injuries and those that initiate the regeneration of the injured neurons. For example, the vascular endothelial growth factors (VEGFs) mediate the recovery process by neurogenesis and increasing vascular permeability, but the VEGFs also have neurotrophic properties and can be involved in tissue regeneration [1, 2]. The matrix metalloproteinases (MMPs) can cause neuronal damage and blood barrier breakdown but they can also play a role in neurovascular remodeling [3]. Tumor necrosis factor-α (TNF-α) and high mobility group box-1 (HMGB1) are effectors of toxic inflammation but can also enhance neurovascular regeneration [4].

During the degenerative process, most mediators enhance the neuronal and vascular cell damage, but during the recovery and regenerating processes, these mediators can be involved in neuroprotection, regeneration, and angiogenesis followed by the final step of tissue remodeling. Thus, an appropriate timing and targeting of these mediators are needed to ensure neurovascular protection.

Neuronal and vascular abnormalities are involved in the pathogenesis and progression of diabetic retinopathy, i.e., pericyte loss and neuronal death occur at the early stage of diabetic retinopathy. Thus, diabetic retinopathy is a good example of a neurovascular disease. Anti-

Toshiyuki Oshitari
Affiliations: Department of Ophthalmology and Visual Science, Chiba University Graduate School of Medicine
Corresponding Author: Toshiyuki Oshitari, MD, PhD., Department of Ophthalmology and Visual Science Chiba University Graduate School of Medicine, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Chiba, Japan; Ph: 81-43-226-2124; Fax: 81-43-224-4162; E-mail: tarii@aol.com or oshitari@faculty.chiba-u.jp

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VEGF drugs are certainly effective in improving diabetic macular edema but chronic and excessive treatment with anti-VEGF antibodies can affect the survival of retinal neurons and remodeling processes because VEGF is an endogenous neurotrophic factor in the retina.

Endoplasmic reticular (ER) stress can cause both pericyte loss and neuronal cell death in diabetic retinas. Thus, anti-ER stress agents such as tauroursodeoxycholic acid (TUDCA) can be used to prevent the onset and progression of diabetic retinopathy [5]. Further studies are needed to establish neurovascular protection in the eyes with diabetic retinopathy.

In routine examinations of the retina, neuronal abnormalities are more difficult to detect than vascular abnormalities, but at a more advanced stage, a reduction in the retinal layer thickness can be clearly seen in the optical coherence tomographic images. Microperimetry may be another method of detecting changes in the physiology of neurons at an early stage.

The important point for ophthalmologists to remember is that most retinal and optic nerve diseases are neurovascular diseases, and the visible pathological changes are only one manifestation of the disease process. For example in eyes with NMO, astrocytes are the main cells affected by the pathological processes of the disease. Ischemic damages of the optic nerve are involved in the pathogenesis of NMO because astrocytes are a major component of the NVUs and are involved in the blood barrier function. Optic nerve abnormalities can be observed by magnetic resonance imaging but vascular abnormalities cannot be observed.

To establish appropriate therapies for neurovascular ocular diseases, single cell and single target therapies will not be sufficient but protecting the NVUs and remodeling, i.e., neurovascular protection, should be considered.

Keywords: Endoplasmic reticular (ER), Glial cells, Neurovascular protection, Neurovascular unit (NVU), Vascular cells

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Conflict of Interest

Authors declare no conflict of interest.

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