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Review

Protecting the retinal neurons from glaucoma: Lowering ocular pressure is not enough☆

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ABSTRACT

The retina is theater of a number of biochemical reactions allowing, within its layers, the conversion of light impulses into electrical signals. The axons of the last neuronal elements, the ganglion cells, form the optic nerve and transfer the signals to the brain. Therefore, an appropriate cellular communication, not only within the different retinal cells, but also between the retina itself and the other brain structures, is fundamental. One of the most diffuse pathologies affecting retinal function and communication, which thus reverberates in the whole visual system, is glaucoma. This insidious disease is characterized by a progressive optic nerve degeneration and sight loss which may finally lead to irreversible blindness. Nevertheless, the progressive nature of this pathology offers an opportunity for therapeutic intervention. To better understand the cellular processes implicated in the development of glaucoma useful to envision a targeted pharmacological strategy, this manuscript first examines the complex cellular and functional organization of the retina and subsequently identifies the targets sensitive to neurodegeneration. Within this context, high ocular pressure represents a key risk factor. However, recent literature findings highlight the concept that lowering ocular pressure is not enough to prevent/slow down glaucomatous damage, suggesting the importance of combining the hypotensive treatment with other pharmacological approaches, such as the use of neuroprotectants. Therefore, this important and more novel aspect is extensively considered in this review, also emphasizing the idea that the neuroprotective strategy should be extended to the entire visual system and not restricted to the retina.

Contents

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1. Introduction

The internal layer of the eye hosts a complex nervous network directly derived from the neuronal crest and containing the photosensitive cells which detect and elaborate light signals: the retina. One of the most diffuse pathologies affecting retinal function, which thus reverberates in the whole visual system, is glaucoma. No matter what the original causes are, glaucoma involves long term and progressive neurodegenerative events implicating a number of retinal cell types and the optic nerve, ultimately leading to sight loss and, in the worst case scenario, to irreversible blindness. Therefore, to better understand the cellular mechanisms underlying the glaucomatous disease, it is initially important to define and describe the fine and subtle cellular and functional organization of the retina, including the relevant transmitters. This background will subsequently allow us to identify the targets sensitive to neurodegeneration, with a particular emphasis on glaucoma, and then build up the rationale for the use of retinal neuroprotectants.

2. The fine cellular structure of the retina

Within the retinal layers, light impulses are converted into electrical signals. The axons of the ganglion cells, the last neuronal elements located in the inner surface of the retina, form the optic nerve and transfer the signals to the brain.

2.1. Cellular populations

The retina (thick ≈0.2 mm) is the first station of the visual system, and it is organized in a number of layers which are able not only to receive light, but also to process the signal through circuits involving a number of classes of cells (see Fig. 1). Indeed, it is possible to recognize the *photoreceptors* present in the Outer Nuclear Layer (ONL), the *bipolar*, the *amacrine*, the *horizontal* and the *Müller cells* whose nuclei are located in the Inner Nuclear Layer (INL) and the *ganglion cells* whose nuclei form the Ganglion Cell Layer (GCL). Moreover, the Outer Plexiform Layer (OPL) contains the processes and the synaptic terminals of the photoreceptors, horizontal and bipolar cells, while the Inner Plexiform Layer (IPL) contains the processes and the terminals of bipolar, amacrine and ganglion cells. Of interest, the *interplexiform cells* are a subtype of retinal amacrine cells which have the peculiar feature of extending their processes into both the inner and outer plexiform layers of the retina [1]. The processes of the Müller cells fill all the space in the retina that is not occupied by neurons and blood vessels [2]. The photoreceptors, the bipolar and the ganglion cells belong to the so called *vertical pathway* of the light signal processing, while the amacrine and the horizontal cells are mainly included in the *horizontal pathway*. The Muller cells represent, instead, the main type of glia present in the retina.

2.2. Photoreceptors

The photoreceptors are located in the outer part of the retina, the region farthest from the incoming light. Therefore, the light has to cross the transparent inner retinal layers before reaching the photoreceptors. Although such an organization may seem counterintuitive, it allows the retinal pigment epithelial (RPE) cells, sandwiched between the retina and the choroids, to absorb the scattered light or the light unabsorbed by the photoreceptors. Moreover, RPE cells also have a supporting role for visual cells, for example they supply nutrients to the retina and perform routine phagocytosis to remove decayed discs of the photoreceptors [3].

Cones and rods are the two types of photoreceptors present in the retina which differ in their morphofunctional properties. Structurally, it is possible to distinguish three main regions: (a) an outer segment, formed by membrane discs, which is specialized in the phototransduction process and contains the visual pigments (conopsin and rhodopsin respectively in cones and rods); (b) an inner segment containing the nucleus and the majority of the cell organelles; (c) a synaptic terminal which allows for contact with bipolar and horizontal cells. The detailed structure and the complex signal (light) transduction of photoreceptors are reported in exhaustive reviews [2–5].

2.3. Bipolar cells

Bipolar cells (BCs) are retinal relay neurons that are critical components of the visual pathway, mainly involving photoreceptors, BCs themselves and retinal ganglion cells (RGCs). In vertebrates,

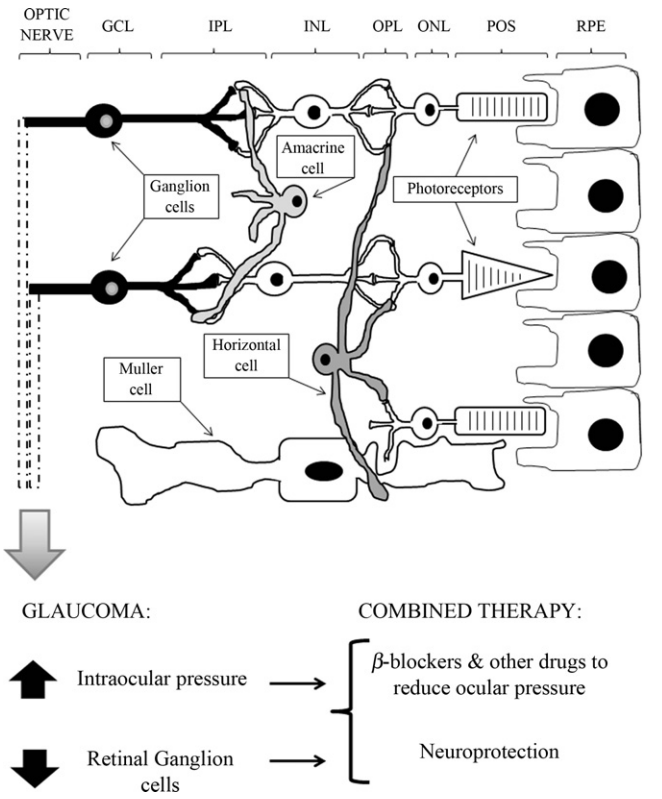

Fig. 1. Schematic representation of the retinal layers with different cell types. RPE: retinal pigment epithelial cells; POS: photoreceptors outer segments; ONL: Outer Nuclear Layer; OPL: Outer Plexiform Layer; INL: Inner Nuclear Layer; IPL: Inner Plexiform Layer; GCL: Ganglion Cell Layer. Modified from [39]. Intraocular pressure increase leads to reduction of retinal ganglion cells finally resulting in the development of glaucoma. Beta-blockers are among the most employed drugs to decrease IOP, although the combined use of neuroprotectants is discussed in the text.