Neuroprotection In Glaucoma

Essay
Submitted for partial fulfillment of Master Degree in Ophthalmology

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List of abbreviations

Arachidonic acid	**AA**
Acetyl-Choline	**Ach**
Asymmetric dimethylarginine	**ADMA**
Advanced Glaucoma Intervention Study	**AGIS**
Apoptosis inducing factor	**AIF**
Adenosine Tri-Phosphate	**ATP**
Brain-derived neurotrophic factor	**BDNF**
Tetrahydrobiopterin	**BH4**
Cup / disc	**C/D**
Calcium	**Ca**
Carbonic anhydrase inhibitor	**CAI**
Cationic amino acid transporter	**CAT**
Calcium Channel Blocker	**CCB**
Collaborative Initial Glaucoma Treatment Study	**CIGTS**
Choroidal neovascularization	**CNV**
Carbon monoxide	**CO**
Confocal scanning laser ophthalmoscope	**CSLO**
Dying Back	**DB**
Docosahexaenoid acids	**DHA**
The Diagnostic Innovations in Glaucoma Study	**DIGS**
Death-inducing signaling complex	**DISC**
Endothelium-derived hyperpolarizing factor	**EDHF**
Endothelium- derived relaxing factor	**EDRF**
Epidermal Growth Factor Receptor	**EGRF**
Endothelin-1	**EN-1**
Erythropoietin	**EPO**
Edinger Westifal Nucleus	**EWN**
Fatty acids	**FA**
Fas-associated death domain protein	**FADD**
Food and Drug Administration	**FDA**
Functional MRI	**Fmri**
Fast nerve fiber layer thickness	**FNFLT**
Ganglion Cell Layer	**GCL**
Scanning laser polarimetry	**GDx**
Geranylgeranylacetone	**GGA**
Glaucomatous optic neuropathy	**GON**
Hypoxia-induced factor 1 alpha	**HIF-1α**
Heidelberg Retinal Tomography	**HRT**
Heat shock proteins	**HSPs**
Hormaonal therapy	**HT**
Inhibitor of Apoptosis Proteins	**IAPs**
Interleukin	**IL**
Inner Nuclear Layer	**INL**
Inner Plexiform Layer	**IPL**
Lateral Geniculate Nucleus	**LGN**
Matrix metalloproteinases	**MMPs**
Magnetic Resonance Imaging	**MRI**
Nicotinamide adenine dinucleotide phosphate	**NADPH**
N - Methyl D - Aspartate	**NMDA**
NO Synthase	**NOS**
Normal tension glaucoma	**NTG**

Ocular blood flow **OBF**
Optical Coherence Tomography **OCT**
Ocular Hypertension Study **OHTS**
Optic Nerve **ON**
Optic Nerve Head **ONH**
Outer Nuclear Layer **ONL**
Outer Plexiform Layer **OPL**
Ocular perfusion pressure **OPP**
Prostaglandin **PG**
Protein kinase C **PKC**
Progressive motor neuronopathy **PMN**
Primary Open Angle Glaucoma **POAG**
Randomized controlled trials **RCTs**
Retinal Ganglion Cells **RGC**
Retinal Nerve Fiber Layer **RNFL**
Retinal Pigment Epithelium **RPE**
Standard automated perimetry **SAP**
Superior cervical ganglion cell **SCG**
Suprachiasmatic nucleus **SCN**
Second Mitochondria - derived Activator of Caspases **SMACs**
Short wavelength automated perimetry **SWAP**
Tricarboxylic acid **TCA**
Tumor Necrosis Factor **TNF**
Tumor Necrosis Factor Receptor **TNFR**
TNF Receptor-Associated Death Domain **TRADD**
Ubiquitin–proteasome system **UPS**
Primary visual cortex **V1**
Vascular Endothelial Growth Factor **VEGF**
Visual Field **VF**
Wallerian Degeneration **WD**

Introduction

A retinal ganglion cell is a type of neuron located near the inner surface (the ganglion cell layer) of the retina of the eye. It receives visual information from photoreceptors via two intermediate neuron types: bipolar cells and amacrine cells. Retinal ganglion cells collectively transmit visual information from the retina to several regions in the thalamus, hypothalamus, and mesencephalon, or midbrain.

Retinal ganglion cells vary significantly in terms of their size, connections, and responses to visual stimulation but they all share the defining property of having a long axon that extends into the brain. These axons form the optic nerve, optic chiasm, and optic tract **(Tabata and Kano, 2002)**.

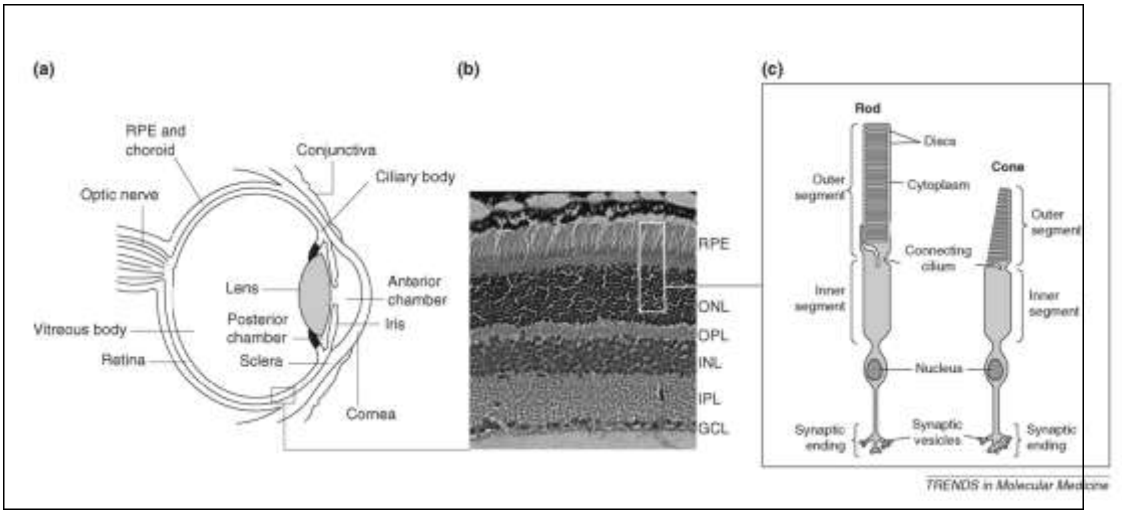

Figure 1. Structural representation of the eye, retinal cells and photoreceptor cells. (a) Schematic representation of the eye structure. (b) Paraffin cross-section (7 mm) of an adult retina stained with hematoxylin and eosin. (c) Scheme representing the structure of rod and cone photoreceptor cells.

Function

There are about 1.2 to 1.5 million retinal ganglion cells in the human retina. With about 105 million photoreceptors per retina, on average each retinal ganglion cell receives inputs from about 100 rods and cones. However, these numbers vary greatly among individuals and as a function of retinal location. In the fovea (center of the retina), a single photoreceptor will communicate with as few as five ganglion cells. In the extreme periphery (ends of the retina), a single ganglion cell will receive information from many thousands of photoreceptors **(Lien and Jonas, 2003).**

Retinal ganglion cells spontaneously fire action potentials at a base rate while at rest. Excitation of retinal ganglion cells results in an increased firing rate while inhibition results in a depressed rate of **(Lien and Jonas, 2003).**

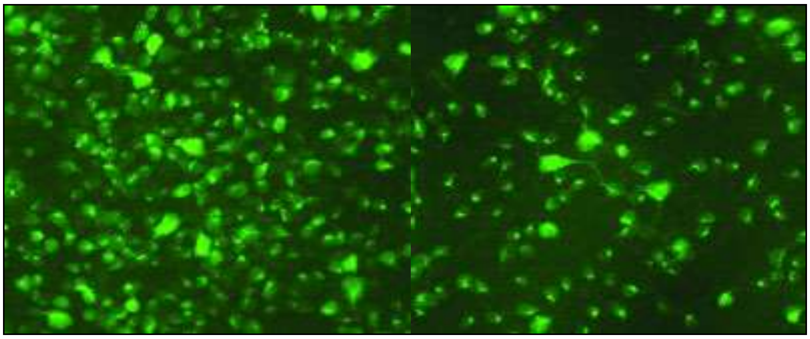

Figure 2. These photomicrographs show Fluoro-Gold–labeled retinal ganglion cells in the central (left) and peripheral retina (right) (both original magnification X400).

Types:

Based on their projections and functions, there are at least five main classes of retinal ganglion cells (**Lee and Ishida, 2007)** :

•Midget (Parvocellular, or P pathway; A cells)
•Parasol (Magnocellular, or M pathway; B cells)
•Bistratified (Koniocellular, or K pathway)
•Other ganglion cells projecting to the superior colliculus for eye movements (saccades) **(Kandel, et al., 2000)**
•Photosensitive ganglion cells

***Midget**

Midget retinal ganglion cells project to the parvocellular layers of the lateral geniculate nucleus. These cells are known as midget retinal ganglion cells, based on the small sizes of their dendritic trees and cell bodies. About 80% of RGCs are midget cells in the parvocellular pathway. They receive inputs from relatively few rods and cones. In many cases, they are connected to midget bipolars, which are linked to one cone each. They have slow conduction velocity, and respond to changes in color but respond only weakly to changes in contrast unless the change is great **(Kandel, et al., 2000).** They have simple center-surround receptive fields, where the center may be either ON or OFF to one of the cones while the surround is the opposite to another cone.

***Parasol**

Parasol retinal ganglion cells project to the magnocellular layers of the lateral geniculate nucleus. These cells are known as parasol retinal ganglion cells, based on the large sizes of their dendritic trees and cell bodies. About 10% of retinal ganglion cells are parasol cells in the magnocellular pathway. They receive inputs from relatively many rods and cones. They have fast conduction velocity, and can respond to low-contrast stimuli, but are not very sensitive to changes in color **(Kandel, et al., 2000).** They have much larger receptive fields which are nonetheless also center-surround.

***Bistratified**

Bistratified retinal ganglion cells project to the koniocellular layers of the lateral geniculate nucleus. Bistratified retinal ganglion cells have been identified only relatively recently. Koniocellular means "cells as small as dust"; their small size made them hard to find. About 10% of retinal ganglion cells are bistratified cells in the koniocellular pathway. They receive inputs from intermediate numbers of rods and cones. They have moderate spatial resolution, moderate conduction velocity, and can respond to moderate-contrast stimuli. They may be involved in color vision. They have very large receptive fields that only have centers (no surrounds) and are always ON to the blue cone and OFF to both the red and green cone **(Kandel, et al., 2000)**.

***Other retinal ganglion cells projecting to the LGN**

Other retinal ganglion cells projecting to the LGN include cells making connections with the Edinger-Westphal nucleus (EWN) for control of the pupillary light reflex and giant retinal ganglion cells **(Kandel, et al., 2000)**.

***Photosensitive ganglion cell**

Photosensitive ganglion cells contain their own photopigment, melanopsin, which makes them respond directly to light even in the absence of rods and cones. They project to the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract for setting and maintaining circadian rhythms **(Kandel et al., 2000)**.

Physiology of the retinal ganglion cells:

Retinal ganglion cells (RGCs) are the only output neurons of the retina of vertebrates. All electrical signals generated by photoreceptors are transmitted by downstream retinal cells and eventually converge onto RGCs. Thus, the physiological function of RGCs is to receive synaptic inputs, to integrate them and transmit the visual information to the central nervous system in the form of trains of spikes.

Intrinsic electrical properties of neurons play a very important role in this postsynaptic integration, so, the continuously updated visual information transmitted to the brain by RGCs is the result of interplay between the extrinsic synaptic inputs and their intrinsic physiological properties **(Mitra and Miller, 2007)** .

The ganglion cell layer:

The ganglion cell layer is a layer of the retina that consists of retinal ganglion cells. In the macula lutea, the layer forms several strata. The cells are somewhat flask-shaped; the rounded internal surface of each resting on the NFL, and sending off an axon which is prolonged into it.

From the opposite end numerous dendrites extend into the inner plexiform layer, where they branch and form flattened arborizations at different levels **(Walia, et al., 2007)**.

The ganglion cells vary much in size, and the dendrites of the smaller ones as a rule arborize in the inner plexiform layer as soon as they enter it; while those of the larger cells ramify close to the inner nuclear layer.