

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	
<u>Heidelberg Retinal Tomography</u>	HRT	
Heat shock proteins	HSPs	
Hormonal 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 neuropathy		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
<u>Suprachiasmatic nucleus</u>	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).

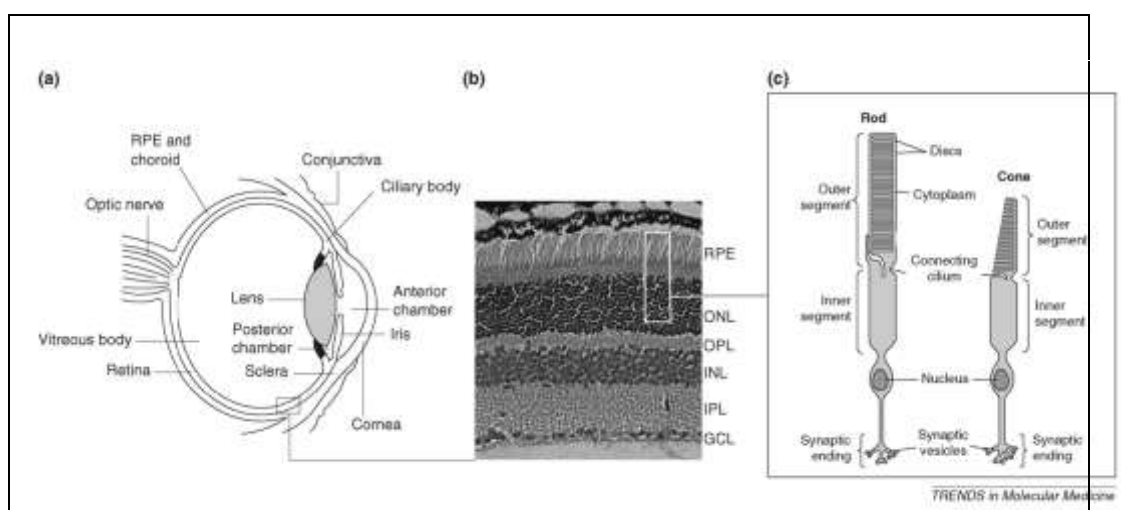


Figure 1. Structural representation of the eye, retinal cells and photoreceptor cells. (a) Schematic representation of the eye structure. (b) Paraffin cross-section (7 mm) of an adult retina stained with hematoxylin and eosin. (c) Scheme representing the structure of rod and cone photoreceptor cells.

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**).

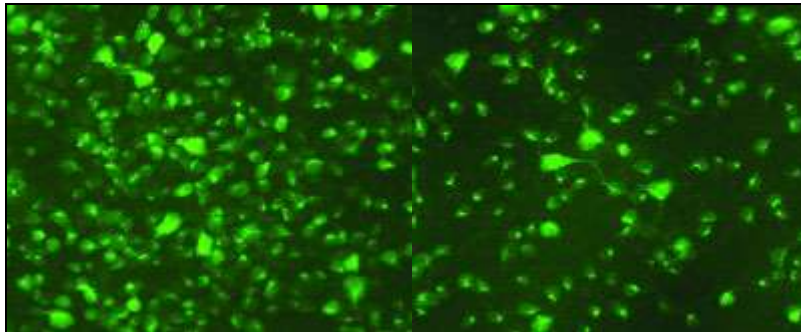


Figure 2. These photomicrographs show Fluoro-Gold–labeled retinal ganglion cells in the central (left) and peripheral retina (right) (both original magnification X400).

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.