

Retinal Prosthesis

Essay

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in Ophthalmology*

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Introduction

Millions of people worldwide lose their photoreceptors either due to retinal degenerations (e. g. retinitis pigmentosa (RP) or age-related macular degeneration (AMD). The feasibility of an implantable retinal prosthesis that would partially restore vision by direct electrical stimulation of retinal neurons is supported by several studies. Morphometric analyses in post-mortem eyes with almost complete photoreceptor loss either due to RP or AMD have shown as many as 90% of the inner retinal neurons remain histologically intact. In tests where electrical stimulating devices were temporarily positioned on the retina, blind subjects reported seeing percepts that corresponded in time and location to the electrical stimulus (*Humayun et al., 2003*).

These systems are based on the electrical stimulation of groups of neurons at several levels of the visual system with multielectrode arrays placed onto or underneath the retina, onto the visual cortex, around the optic nerve, on the sclera or in the suprachoroidal space. The history of artificial vision began when Brindley implanted several electrical stimulators close to the visual cortex in a woman who was blind due to retinitis pigmentosa (RP). After surgery, this patient was able to see spots of lights—electrically evoked phosphenes. Large efforts were undertaken to characterize the kind of phosphenes that were elicited with this system. The Brindley approach was later continued by Dobelle, who implanted several patients with his

cortical stimulator. The stimulator was connected to an external power source and to a visual processor with a cable.

The information for the visual processor was taken from a camera chip mounted on one glass of spectacles and from an ultrasound sensor giving distance information. The Dobelle group reported that the patients were able to see phosphenes, to identify obstacles and to recognize high contrast objects (*Walter et al.,2005*).

The final goal of artificial vision is not to elicit phosphenes, but to restore vision with spatial and temporal properties similar to natural vision, vision that can be used by blind individuals to improve their daily life and performance, not only to restore spatial and temporal resolution in a picture, but also to restore the emotional content of vision, such as the recognition of a beautiful landscape, a colorful sunset or the face of a beloved friend, to make them also be able to participate in the emotional side of our visually dominated life (*Walter et al.,2005*).

Aim of the Work

- Is to review the different types of retinal prosthesis.
- Role of retinal prosthesis in management of retinal disorders.
- Current status of retinal prosthesis in our clinical practice.

Physiology of Vision

The sense of vision is a very complex sense involving several processes that occur simultaneously to allow us to perceive the world around us. Special light-sensitive photoreceptors (some able to distinguish differences in the wavelength or color of light) are present in the retina of the eye. Other structures such as the lens and cornea gather the light entering the eye and bend or refract that light to form a clear image so that we can distinguish size, shape, and form. The iris adjusts the intensity of light by adjusting pupil size so that the image is neither too dark nor too bright. Extrinsic eye muscles work so that both eyes are directed to the same point. Finally, the information from the photoreceptors must be directed to the brain where this information can be processed. All these processes must be occurring correctly in order to experience normal vision. Disruptions or abnormalities of any of the structures of the eye can cause visual impairment.

The retina is derived embryologically from the optic vesicle, an outpouching of the embryonic forebrain. The bilayered neuroepithelial structure of the mature retina reflects the apex-to-apex arrangement of the original optic cup. Since the cell apices are oriented inwardly, the two layers of the optic cup and their derivatives are enveloped externally by basement membrane (*Schubert et al., 2008*).

The relationship of the epithelial layers to each other is modified from anterior to posterior. Anterior to the ora serrata, the pigmented and nonpigmented epithelia of the iris and ciliary body are joined at their apices by a system of intercellular junctions (Figure 1), which is continuous with the external limiting layer of the neural retina and the apical junctional girdles of the retinal pigment epithelium (RPE). At the ora serrata, the pigmented epithelium is continued as RPE; its basement membrane becomes Bruch's membrane. The nonpigmented epithelium of the ciliary body and pars plana is continued posteriorly as the neural retina; its basement membrane becomes the internal limiting membrane. The union of the epithelial layers delimits the anterior cul-de-sac of the subretinal space (**Schubert et al., 2008**).

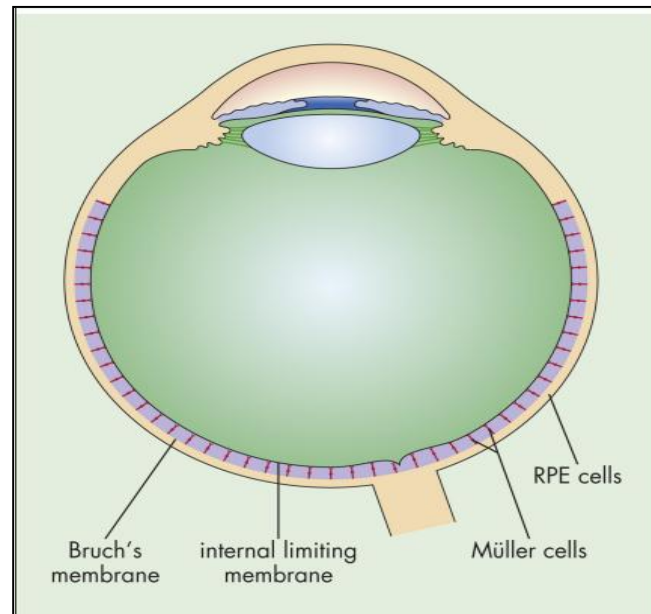


Figure (1): Apex-to-apex arrangement of müllerian glia and retinal pigment epithelial cells. Because the cell apices face each other, the neuroepithelia are enveloped externally by a basement membrane. Note that this basement membrane is elaborated by a single-layer neuroepithelium, with the exception of the internal limiting membrane, which is formed by Müller cells (*Schubert et al., 2008*).

The apex-to-apex arrangement between the epithelia that clearly exists anterior to the ora is continued posteriorly by Müller cells that face and intermittently contact the RPE (Figure 2). Here, the contact is maintained not by apical junctions (even though an inter-receptor matrix exists) but by the pressure of the vitreous and by suction forces of the RPE. Müllerian glia are the main structural cells of the neural retina

and are found throughout the retina from the ora to the optic nerve head (*Schubert et al., 2008*).

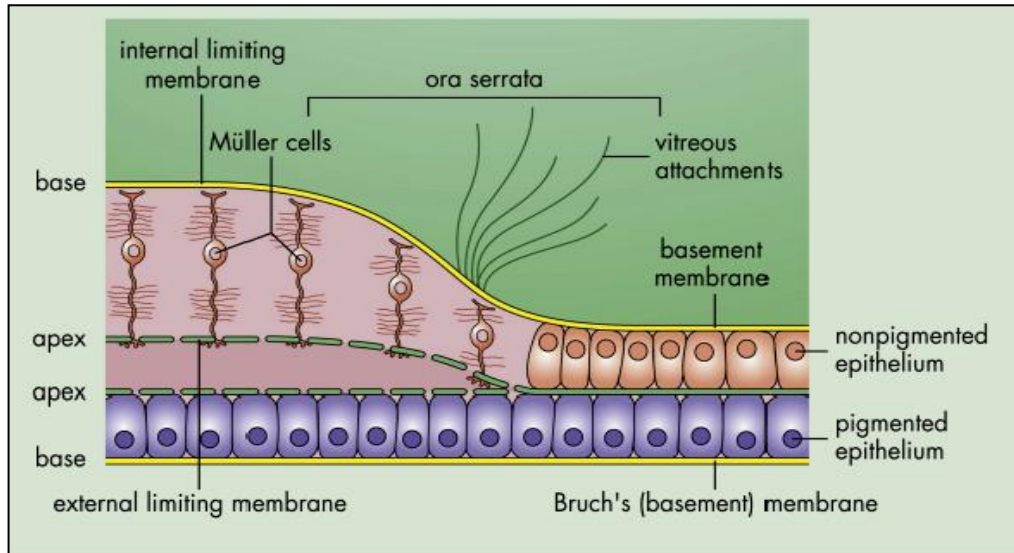


Figure (2): Transition of neural retina to nonpigmented epithelium at the ora serrata. The external limiting membrane, which consists of the attachment sites of photoreceptors and Müller cells, transforms into the apical junctional system of the pars plana epithelia. The internal limiting membrane becomes the basement membrane of the nonpigmented epithelium (*Schubert et al., 2008*).

The retina consists of a thin tissue of multiple cell layers containing both receptors (rods and cones) and neurons (amacrine, bipolar, interplexiform and ganglion cells). The retina also contains astrocytes called (Müller cells) that actively participate in Na^+ and K^+ ionic transport. The retina is a complex brain structure that not only transduces visual signals into neural signals but also begins the processing of visual information.

The photoreceptor cells of the retina are the sensory transducers for visual system, they function to convert electromagnetic energy (light) into a neural signal. The photoreceptors contain visual pigments which by absorbing photons of light initiate the phototransduction process. These visual pigments have evolved to absorb within the range of electromagnetic wavelengths that pass through the cornea and lens, generally between 400 and 700 nm.

Rods function for night vision whereas cones function for daytime and color vision (*Celesia et al., 1994*).

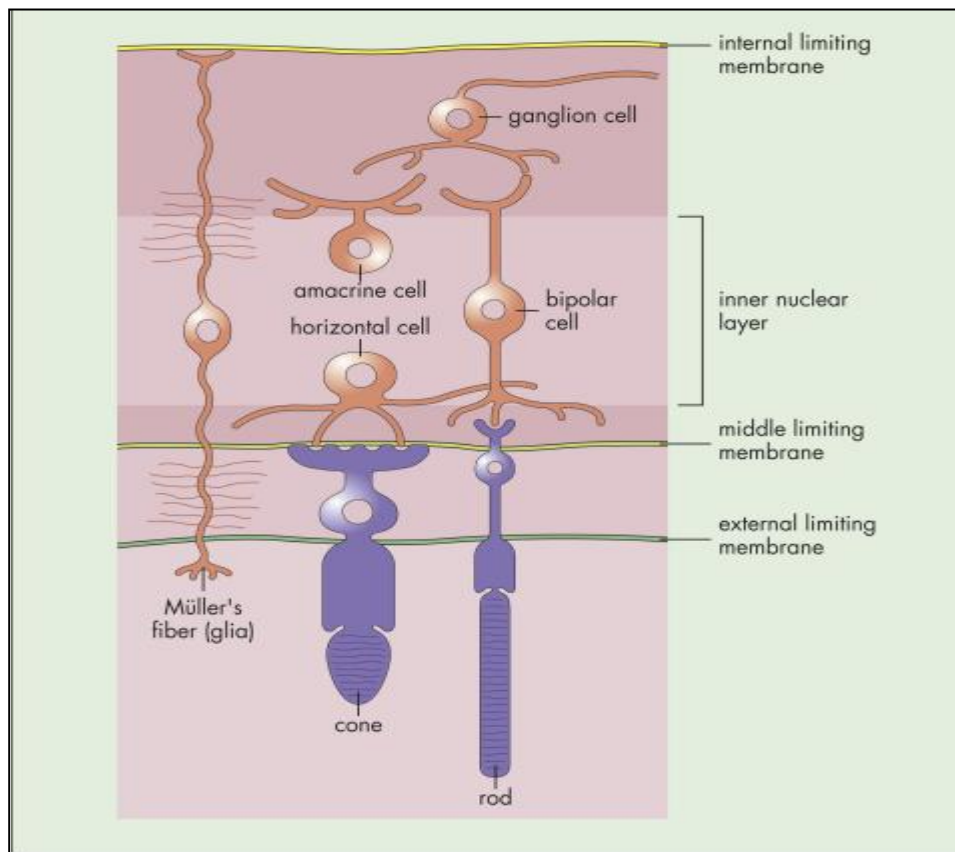


Figure (3): Neuronal connections in the retina and participating cells. The inner nuclear layer contains the nuclei of the bipolar cells (second

neuron) and müllerian glia. The amacrine cells are found on the inside and the horizontal cells on the outside of this layer, next to their respective plexiform connections (**Schubert et al., 2008**).

Rod and cone photoreceptors are easily distinguished by their outer segments. The outer segment contains photopigment in free-floating disks (rods) or folded layers (cones). Cone outer segments have a continuous outer membrane, whereas rods have discs, stacked like coins, in a sleeve.

Inner Segment: Photoreceptor inner segments contain the nucleus, support organelles (mitochondria, ribosomes, endoplasmic reticulum, synaptic vesicles, etc.), and the axon terminal (where neurotransmitter is released). The capture of individual photons by the photopigment molecules in the disk membranes is what initiates neural signalling.

Photoreceptors are actually specialized hair cells, and the inner and outer segments are connected by the cilium (**Celesia et al., 1994**).

The human retina contains approximately 120 million rod and 1 million cone photoreceptors. Cone density is highest at the fovea, Rods are actually absent in fovea.

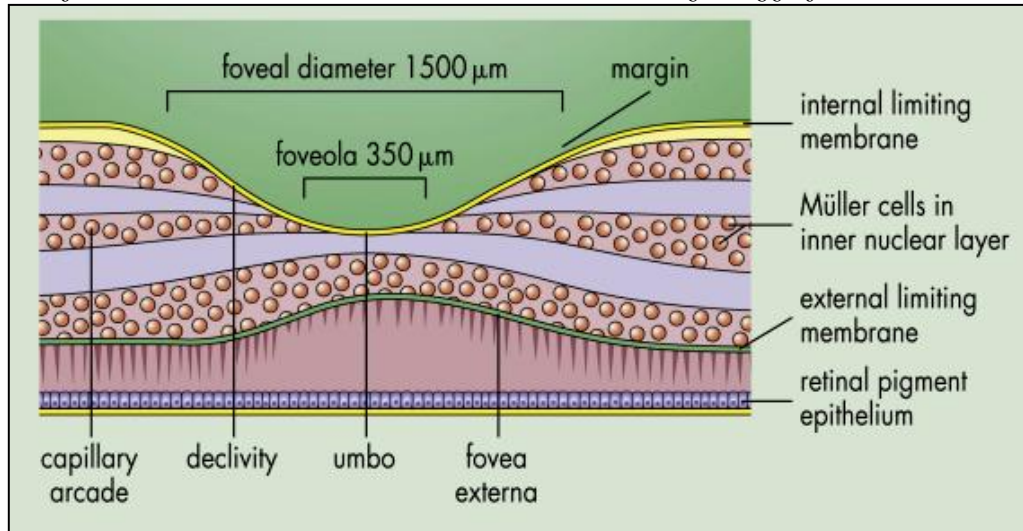


Figure (4): Foveal margin, foveal declivity, foveola, and umbo (*Schubert et al., 2008*).

Photoreceptors are in a depolarized state in the dark caused mainly by the influx of Na^+ ions across the cell membrane and partially to the movement of Ca^{2+} and Mg^{2+} ions as well. Rods and cones hyperpolarize producing graded response that depends on the intensity of light.

Hyperpolarization of the photoreceptor outer segment and subsequent release of neurotransmitter by the inner segment is controlled by cyclic guanosine monophosphate (cGMP) second messenger system. The response of photo-receptor to light is a function of both the wavelength and intensity of light.

The wavelength of light that maximally stimulates the photoreceptors is determined by the spectral sensitivity of the photopigment contained in its outer segment. Humans have

4 types of photopigments in their retina ,one in rods and 3 in cones (*Celesia et al.,1994*).

When the photoreceptors respond to light, the potassium concentration falls for a few seconds in the subneural retinal space. The apical membranes of the RPE and the Müller cells respond by hyperpolarizing, which produces the c wave of the electroretinogram. This potassium change is transmitted slowly through the RPE cell, and roughly 1 minute later, a hyperpolarization appears at the basal membrane, which accounts for the “fast oscillation” of the electro-oculogram (EOG). This response involves basal chloride channels and is abnormal in some patients who have cystic fibrosis. Light activation of photoreceptors also causes the release of an unknown messenger substance that causes a basal RPE depolarization 5–10 minutes after the onset of light activation. This late basal depolarization is recorded clinically as the “light response” of the standing potential in the clinical EOG (*Marmor et al., 2008*).

Absorption of light in the photoreceptors converts 11-*cis* vitamin A to the all-*trans* form, which initiates the process of transduction and begins a series of regenerative chemical changes that are independent of vision. Vitamin A is split off from the opsin molecule and carried by a transport protein to the RPE. In the RPE, vitamin A may be stored in an ester form, but eventually it is isomerized back to the 11-*cis* form and recombined with opsin. The RPE is vital for this process and

for the capture of vitamin A from the bloodstream to maintain its concentration within the eye. Defects in several genes that control this regenerative cycle in the RPE can cause retinitis pigmentosa, such as the gene for retinaldehyde binding protein (RLBP) and the RPE65 gene (involved in 11-*cis* retinol metabolism) (*Marmor et al., 2008*).

Phototransduction step by step

In the absence of light, the photoreceptors are depolarized to a membrane resting potential of -40mV. Light will hyperpolarize the plasma membrane of the photoreceptor to -70mV (Figure5). This stimulus-induced hyperpolarization is a distinctive characteristic of the photoreceptor response, as many other neuronal types depolarize when stimulated.

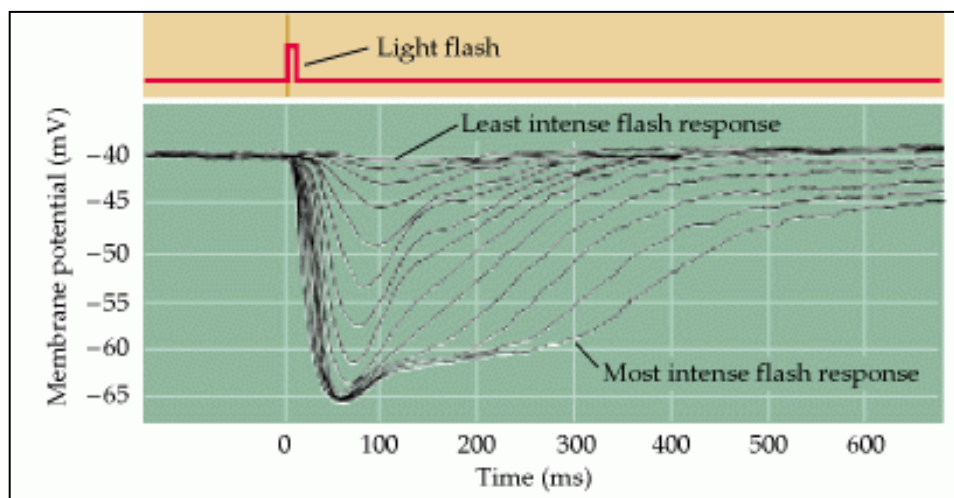


Figure (5): An intracellular recording from a single cone stimulated with different amounts of light. Each trace represents the response to a brief flash that was varied in intensity. At the highest light levels, the response amplitude saturates (*Neuroscience et al., 2001*).

A key second messenger molecule responsible for maintaining a depolarized rest state in photoreceptors is the nucleotide cyclic guanosine 3'-5' monophosphate (cGMP). High cGMP levels keep cGMP-gated ion channels in the open state and allow them to pass an inward Na^+ current (Figure 6).

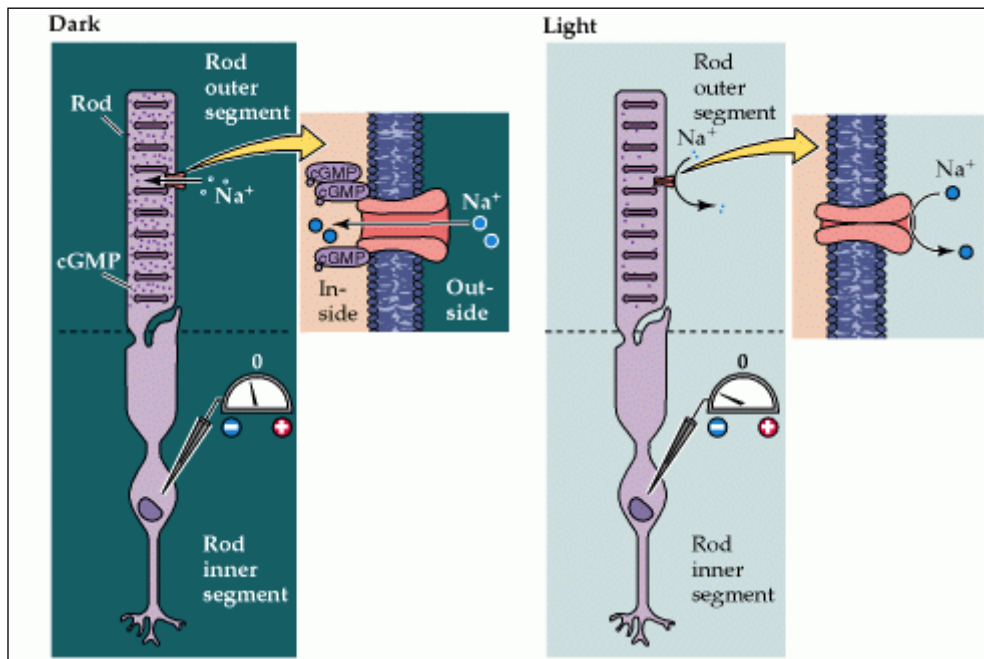


Figure (6): Cyclic GMP-gated channels in the outer segment membrane are responsible for the light-induced changes in the electrical activity of photoreceptors (*Neuroscience et al., 2001*).

Phototransduction involves three main biochemical events:

Light entering the eye activates the opsin molecules in the photoreceptors:

Upon photon absorption, 11-*cis*-retinal undergoes an isomerization to the all-*trans* form, causing a conformational

change in the rhodopsin. The activated rhodopsin is called metarhodopsin II.

The precursor for 11-*cis*-retinal is all-*trans*-retinol (vitamin A). A diet rich in vitamin A is crucial for vision, since vitamin A cannot be synthesized by humans.

Activated rhodopsin causes a reduction in the cGMP intracellular concentration:

The cytoplasmic cGMP levels are controlled by cGMP phosphodiesterase, an enzyme that breaks down cGMP. In the dark, the activity of this enzyme is relatively weak. When the photoreceptor is exposed to light, metarhodopsin II stimulates the activity of cGMP phosphodiesterase via transducin, a G protein. GDP-bound inactive transducin will exchange GDP for GTP following interaction with activated rhodopsin. GTP-bound active transducin will increase the activity of cGMP phosphodiesterase. The result is decreased levels of cGMP in the cytoplasm.

The photoreceptor is hyperpolarized following exposure to light:

Decreased levels of cGMP cause the closing of cGMP-gated ion channels which will lead to membrane hyperpolarization.

Figure (7) summarizes the phototransduction cascade.