Review

Morpho-functional Novelties Concerning the Retina and Visual Prosthesis

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ABSTRACT The technological development in the last decade led to advances in the study of the retina. Using new techniques of immunohistochemistry and miniature electrodes, several new subtypes of cells and their functions were detected. These discoveries allowed researches to better describe the data processing that occurs at retinal level and to create superior models of this particular neural structure. Because of this accumulation of essential information about the way retina works, several attempts of replicating its behaviour are under developent. At this moment there are several research teams trying to create a fully functional visual prosthesis. Among these, two are most successful, one from Germany, using a subretinal implant, and one from the Unite States, using an epiretinal implant.

KEY WORDS *retina, discovery, cells, implant, visual prosthesis*

Introduction

Without a doubt, the visual analyzer is one of the first and most studied components of the human body. If the theories of the ancients make us smile at this moment, because they believed that the eye "threw" rays which captured the image of the object seen, since 1600 the foundations of the modern theory of vision have already been laid. The two events which led to this true revolution are the description done by Johannes Kepler of the optic system and of the mechanism of formation of images, and the experimental demonstration that images are created on the posterior wall of the eyeball done by Christopher Scheiner. Until the late 17th century there have been described parts of the retina (Leeuwenhoek, Briggs), it was suggested that the images are projected to the brain (Descartes, Willis) and there have been formulated the corpuscular (Newton) and wave (Huygens) theories of the propagation of light, as well as the laws of reflections, refraction, dispersion and diffraction [29].

From these beginnings the advance has been enormous in describing the structure of the eye, how images are formed on the retina and what their projections in the cortex are, with outstanding contributions by Muller (he demonstrated that photoreception occurs in the cone and rod cells), Young-Helmholtz (trichromatic theory of vision) and Ramon y Cajal (the first complete description of retinal neuroanatomy), to name just a few of the most renowned researchers in the field [29]. At this point, research on the visual analyzer has two main areas: the detailed studies of retinal components and the studies of the way in which images are formed and processed centrally.

In order to review the current progress in identifying retinal elements and their roles, we consider that it is essential to remind the organization and general functioning of the retina.

The retina is classically described as having 10 functional layers (fig.1a). In these layers we encounter seven types of cells (fig.1.b) in synaptic relationship between them. Retinal cells are photoreceptor cells (two distinct types, the rods and cones), bipolar cells and ganglion or multipolar cells, plus association cells - horizontal cells and amacrine cells and supporting cells - Müller glial cells. Some cell types (e.g. ganglion or amacrine cells) have many subtypes, with more functional than morphological differences [21].

Rod cells are modified nerve cells, they are about 125 millions, and they are more numerous towards the periphery of the optic retina. The macula lutea contains just a small number of them, and they are missing in the fovea centralis. Rods are adapted for night vision, for dim or twilight light. In the peripheral area of the retina many rod cells have synapses with a single bipolar cell, and more bipolar cells have synapses with a single ganglion cell, so that to a ganglion cells receives inputs from 90 to 180 rod cells. Cone cells are also modified nerve cells, numbering about 5.5 millions. They are more numerous than rods in the macula lutea. The fovea centralis is made only of cone cells, which form synapse with two bipolar cells, and each of these with one ganglion cell.

Retinal ganglion cells are the only neurons that transmit visual signals as action potentials by obeying the law "all or nothing." These cells send all the information to the brain. In contrast, all other retinal neurons, including photoreceptor cells, lead the visual signals through electrotonic conduction. Electrotonic conduction means the movement of electrical charge through the neuronal cytoplasm, having a gradual response rather than an action potential. Thus, for the rods and cones, the signal output is directly related to the intensity of light.

The technological development in recent decades has allowed the emergence of new equipment and techniques with applications in the study of retinal microelements, as well as more accurate data on the processing of the information at this level. From this point of view we consider it is important to make an overview of the key scientific advances in this area, namely the discovery of new subtypes of retinal cells and the development of theoretical models and simulations of the retinal activity in order to create "visual prosthetics".

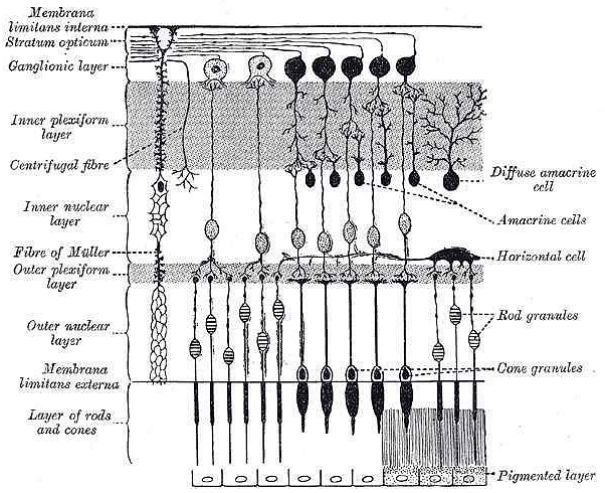

Fig.1 a. The layers of the retina (Gray)

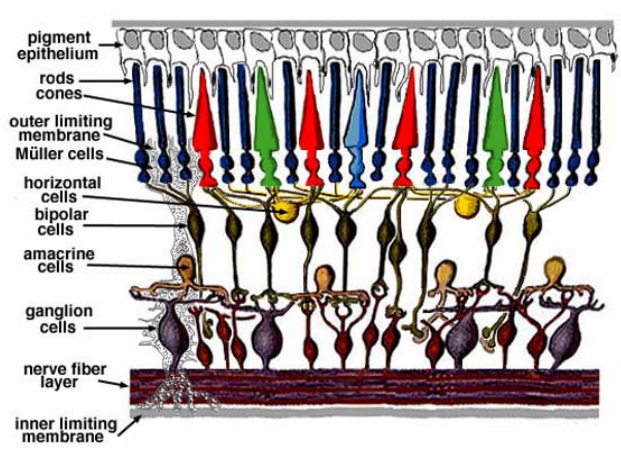

Fig.1 b. Types of retinal cells (Kolb[21])

Findings of new types of retinal cells

The recent years are characterized by identifying and describing new retinal cell subpopulations, which are evidenced only now because of new techniques of immunohistochemistry or extreme miniaturization of the electrodes required for recording activity of individual neurons.

No later than in 2009 a German team published results [9] describing new interplexiform "ON" amacrine cells in mice. These cells, which were called IPA-S4 / 5, do not use GABA as neurotransmitter dopamine and express the GAT-1 gene, resulting in the appearance of a plasma-membrane GABA transporter, probably involved in non-vesicular release of GABA. Response to light of these cells is consistent with their position in the ON sublamina of the internal plexiform layer, being depolarized by "light ON" type and hyperpolarized by "light OFF" stimuli. The response of these cells to green light (578 nm) and blue (400 nm) suggests that they receive information from bipolar cells connected to S and M cone cells.

Although the retina has traditionally been regarded as a simple filter through which the visual world is transmitted from eye to brain, several discoveries made in the recent years have changed this picture: it was proved that the retina performs advanced processing of the visual information and sends a very selective form of this information to the brain.

Researchers from the teams of Rava Azeredo da Silveira (Statistik Laboratoire of Physique, Ecole Normale Supérieure, Université Paris Diderot) and Botond Roska (Friedrich-Miescher Institute) identified in 2009, a new type of cell, actually a subpopulation of ganglion cells retina in mice, called PV-5, responsible for detecting approaching objects [22]. They are activated when an object in the visual field seems to grow in size, but non responsive if the motion is sideways or away. Thus, these nerve cells send a warning signal to the brain when, for example, a predator approaches, and are therefore is essential for survival. The discovery of this new type of cells was made possible by experimental isolation of the neurons in question, and of relevant neural circuits.

For the “approaching motion detection” function the retinal neurons in this circuit use a rapid inhibitory neural pathway that suppresses any response to a stimulus other than the movement nearby. Although this inhibitory pathway has been identified as being involved in nocturnal vision, here this pathway is used for

sending signals backwards during diurnal vision, from amacrine cells to bipolar cells. It is therefore an effective example of adaptation, because in evolution, the same neural circuit has different functions depending on the physiological conditions to which it is exposed.

In the experiments done the teams have used transgenic mice that had certain types of ganglion cells marked using EYFP (enhanced yellow fluorescent protein). Stimulation was made by presenting images showing black bars that simulate approach (increase in size), departure (decrease in size) or move laterally after being displayed for 2 seconds in advance. It was found that only bars increasing caused massive spike generation in PV-5 type ganglion cells, with a growth rate that depends on the speed of movement of the bar, without substantial change during motion with constant speed.

In this study, which combines various experimental methods, genetic marking of cell types, high-resolution microscopy (TPM - two photons microscopy) and electrophysiological methods were accompanied by an approach based on theoretical modelling. This illustrates the complementarities of practice and theory as required for quantitative biology findings using methodological tools from mathematics, statistics and research based on experiment.

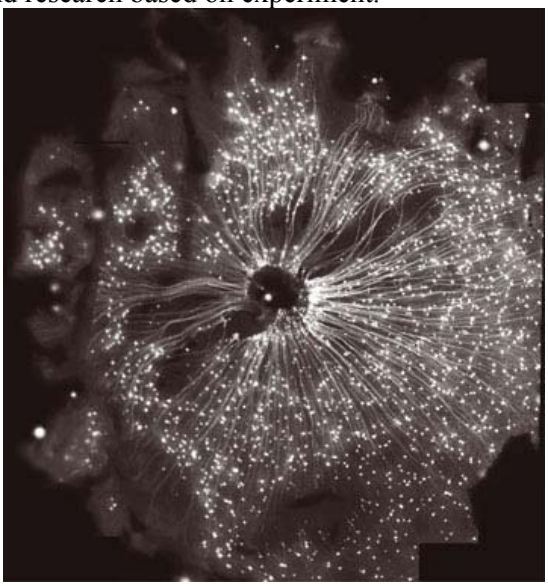

Fig.2a.Image of a mouse retina with ganglion cells sensitive to approaching movement marked. Cell bodies are white dots, axons are lines converging to the optic disc, from where the optic nerve goes to the brain [22]

Regarding the retinal cell overspecialization and the complexity of neural circuits at this level, it should be noted that some ganglion cells respond to differential movement between the central and peripheral receptor field, such as that produced by a moving object in the background, but are strongly inhibited by the global movement of the image, e.g. when the observer moves his eyes or head [5]. These cells have been identified in 2003, and in 2008 it was identified the neural circuit that produces stimulation of this cell type known as OMS (object motion sensitive) by intracellular recordings from all classes of retinal interneurons while simultaneously recording spikes generated by various subpopulations of ganglion cells [23]. Rapidly, bipolar cells respond linearly to motion in the centre of the receptive field. Their synaptic output signal is corrected and then gathered by OMS ganglion cells. One type of poliaxonale amacrine cells are stimulated by movement occurring in the periphery, again corrected by multiple stimuli, but from other axonal endings of bipolar cells. By direct intracellular electrical stimulation, researchers have found that these amacrine cells selectively suppress the synaptic input of poliaxonale OMS ganglion cells. Researchers have developed a quantitative model of these neural circuit elements and their interactions, which explains how this visual information processing is performed by retinal neurons and the synapses between them.

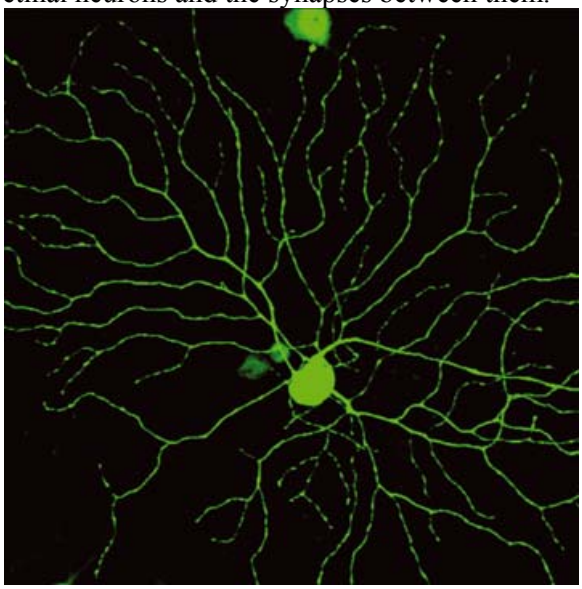

Fig.2b.Morphology of the cell body and dendrites of ganglion cells responsible for detecting approaching objects [22]

Scientists admit that in the retina of primates there are at least 22 types of morphologically distinct retinal ganglion cells, but until now only six of them have been physiologically described.

In April 2008, researchers at Harvard University, Massachusetts announced [20] the discovery of a new type of retinal ganglion cell, which plays an exclusive and unusual role in mice: detecting upward motion. Its function is

reflected in the arrangement of its dendrites, which have the same direction in proportion of 90%, and not the classical, radial layout.

In 2008 a research team composed of physicists from the University of Santa Cruz, California, and neuroscientists from the Salk Institute in La Jolla, California, discovered a type of retinal cells that can are used by monkeys, apes and humans in motion detection [24]. This cell type has very similar properties to the so-called Y retinal ganglion cells, which were first described in cats in 1966; after the discovery of the Y cell, scientists began a search that lasted nearly four decades of its counterpart primates. The team called the new cell type "Upsilon", named after the Greek letter "Y".

The identification of such cells was possible using a new type of microelectrode system for large-scale recordings of neural activity. In these experiments it was proven the existence of a cell population with distinct physiological properties of other ganglion cells in terms of response to visual stimulation. This type of ganglion cells is characterized by an extremely large size of the dendrites compared with other subtypes of ganglion cells, which allows the collection of information from a much larger retinal area. This is how they are able to serve as a processing unit for visual information in order to generate messages on moving objects on the visual field. These cells generate quick answers that do not persist long.

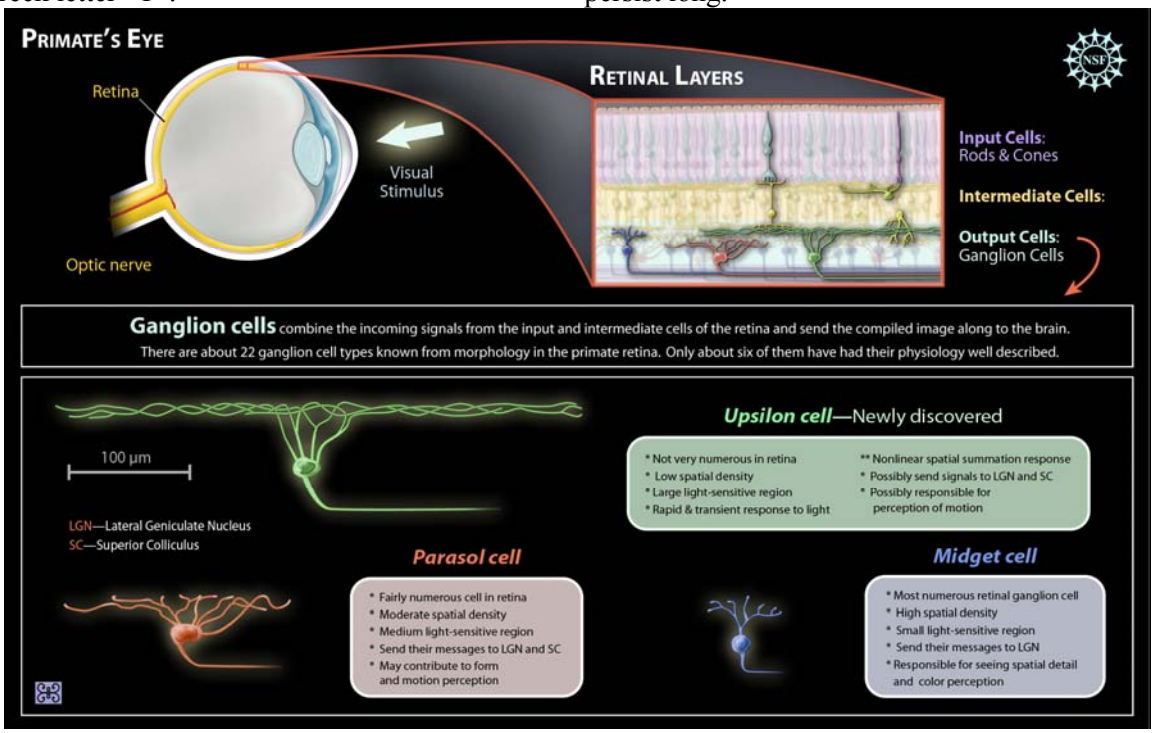

Fig.3. The Upsilon ganglion cells[24]

In 2007 there were identified in humans too intrinsic photoreceptor ganglion cells [30], which have the main role in regulation of circadian rhythms. Their photoreceptor substance is a new opsin, which was isolated and identified only in 2000 by [25] one of the researchers who discovered back in 1991, in mice, these particular ganglion cells, through experiments involving induced retinal degeneration [13].

Theoretical models of retinal activity

The way information is processed in the retina and in reaching the integration areas of the cortex is still incompletely understood. Although we know the most important principles of this mechanism, the details are not yet mastered.

In 2007, Frank Werblin and Botond Roska from Berkeley, California published [27] a paper explaining how from the retina 12 different sequences that characterize a single image are transmitted simultaneously, but separately. Each sequence is generated by a particular population of highly specialized retinal cells, cells that have their own fibres in the optic nerve and that are related to cortical areas where further processing and signal integration occurs. At a central level there is a recombination of these separate fluxes of information, pure optical information being recombined with information related to object movement and recognition. The paper is based on experiments that date back to 2001 [26].

The same Frank Werblin, along with Shelley Fried and H. A. Hsueh, managed in 2006, by

epiretineal stimulation with electrical impulses sent to the ganglion cells, through microelectrodes, to induce the appearance of spikes from these cells [14], which then spreads via the optic nerve. If the stimulation is made with pulses greater than or equal to 1 ms, there are generated spike trains longer than 100ms, while using pulses of less than 0.15ms the response obtained is a single spike. Using this kind of short pulses, pulse trains with frequency of less than or equal to 250 Hz continued to generate only one spike per impulse. Pulse patterns derived from the action of light onto the ganglion cells generated spike discharge patterns that replicated spikes given by normal light. As a conclusion, they have shown that this type of electrical stimuli can be used in visual prosthesis. Fried, together with other collaborators (e.g. Masland, 2007) showed how retinal cells, mainly "starburst" amacrine cells help to encode information about the movement direction of objects in the visual field, information submitted to the cortex by "directional selective" ganglion cells - DS [15].

Frank Werblin and his close collaborators (B. Roska and his father, T. Roska), together with D. Balya published concepts related to a theoretical model for the functioning of biological sensory systems, with the main model being the retina [6,7]. Their studies are based on the CNN (cellular neural networks), a customizable artificial neural networks designed by Leon Chua, Lee Yang (1988) with Tamas Roska (1993).They are based on simple computational elements (artificial neurons), interconnected in the framework of multilayer networks. In a CNN interaction is allowed only between adjacent units within a radius of **r** units, and only from this description there already are obvious similarities with the retina. The proposed model defines different types of receptor neurons grouped into separate layers, which receive information from the underlying neurons (synapses) and use a minimum of parameters: a time bound constant, the local links within the layers and the continuous output function. These abstract neurons have three types of receptors, corresponding to three types of synapses: normal, delayed and desensitized.

Development of "visual prosthesis"

Due to the rapid advance of technology, the research field of visual prosthesis benefits of accumulation of essential information in recent years. What is more important, these discoveries turn into new techniques, some already with therapeutic applications, such as the establishment of the first "artificial retina" [1] – the retinal implants ARGUS ™ (used between 2002-2004) and ARGUS II ™ (approved for clinical testing by the FDA in February 2008 [2] and used successfully for the first time in Europe in April 2008 [3], in Great Britain).

There are over 20 independent groups [4] worldwide that have the goal to develop an implant capable to allow blind people a partial recovery of visual sensation and at least to improve spatial orientation. At this moment some of these groups, from the U.S. and Germany, have reached the stage of clinical testing with human subjects.

A common characteristic of these implants is the shunting of the destroyed or degenerated retinal layers and direct stimulation, by electrical impulses or neurotransmitters, of the functional visual pathway. There are two distinct approaches in terms of the implant's localization: subretinal and epiretinal. Epiretinal implant studies use an array of up to 64 microelectrodes (micro array), which receive visual information from external devices. Subretinal devices have up to 5,000 micro photodiodes and amplifiers placed directly under the retina, that convert the image naturally formed in the eye in a proper sequence of electrical signals.

In 2005, in a pilot clinical study led by Professor E. Zrenner, early subretinal chips were implanted in blind at the University of Tubingen, which works with a private company, Retina Implant, a result of work of a consortium of universities and hospitals Germany [16, 19]. So far, 11 patients were temporarily implanted with this device, which is extracted after 4 months for detailed study of the area affected and to prevent local complications. A first implantation does not exclude a second one, even on the same eye. After improving the model, future versions will be left in place for much longer periods, permanently if possible. At this time patients can require the implant not to be removed, but they do so at your own risk.

The main part of the implant consists of a microchip approx 3mm in diameter with a thickness of 50 μm, which has about 1,500 receptive fields (pixels), with the size of 70 x 70 μm. Each field has a photocell, an amplifier circuit and a stimulation electrode. Photocells absorb light entering the eye, transforming it into electrical signals. An external power source located behind the ear allows amplification of the generated signal and the power of this signal modulates the amount of power released by the electrodes to stimulate retinal nerve cells remained intact. Nerve impulses are further processed by the

natural retinal neuronal network and transmitted through the optic nerve to the visual cortex, creating visual sensations.

From 2000 until 2004 there was a clinical trial with a device created by the company Optobionics, the leader of this team being Professor Alan Chow [8]. Their device, 2mm in diameter and 25 mm thick, consists of a diode array equipped with approximately 5000 microelectrodes, using only incident light to generate electrical stimuli. This way it was proven that a passive device is feasible. A connection with an external energy source is not necessary, thus decreasing the risk of complications (infection, inflammation, neovascularization, migration, etc.). The device was implanted in six patients with retinitis pigmentosa for periods between 6 and 18 months in the right eye while the left eye was used for comparing results. Surprisingly, besides improving the sensation of brightness, contrast, colour, movement, shape and size of the visual field, it was found an improvement of retinal activity in areas far from the implant. So far 42 patients suffering from retinitis pigmentosa have been implanted.

Another advanced team in this field [18] is that of Professor Joseph Rizzo (Associate Professor of Ophthalmology, Harvard Medical School, Boston, MA) and John L. Wyatt (MIT, Cambridge, MA). Although initially focused on epiretinal stimulation and even making simulations with intraocular electrodes in 6 patients, they finally produced a subretinal stimulation device, which consists of a microcontroller embedded in a titanium casing that is fixed under the conjunctiva, with an energy source on contact lens. In 2008 this device was tested on laboratory animals (two of Yucatan mini pigs) for 3 and 5.5 months, when it was removed due to damage superjacent conjunctiva. The causes that led to these problems were identified, the implant has been modified to correct them, and new tests will be performed to observe the length of use of this implant without complications. However, the tests done until now can be considered successful, because after the implant was powered and data communication to the implant was made, recordings that show stimulation of nerve elements have been done.

There are other teams that have already prepared subretinal implants, but they haven't reached yet the stage of testing it on humans, but only on primates (e.g. Professor H. Gerding's team, Switzerland-Germany [17]).

Certainly the most successful research group at this moment is an American team, Second Sight, which is strongly supported by the U.S. Department of Energy, National Institutes of Health / National Eye Institute and the Doheny Eye Institute [10.11, 12].

The Argus retinal implant produced by this company is a micro array of electrodes that attaches to the retina and is used with an external camera and an image processing unit to provide a rudimentary form of vision for the subject. The video camera takes the picture and transmits it to a processing system embedded in a device worn by the subject. Information, processed and represented as pulses, is transmitted via radio waves to a chip that is connected to the microelectrodes that stimulate the nerve cells in the visual transmission pathway. ARGUS II, the second generation retinal prosthesis system, can provide visual sensation - light detection - for those who have become blind because of degenerative eye diseases such as macular degeneration and retinitis pigmentosa. Its main part is a micro array of 60 epiretinal electrodes, a huge improvement over the 16 microelectrodes of the first model. For this system to function, a healthy, functional optic pathway is needed to transmit the information to the cortical level, because the implant is doing nothing more than replace the photoreceptor elements in the retina. Because of differences from the natural stimuli, patients must learn to interpret the new stimuli as visual sensations.

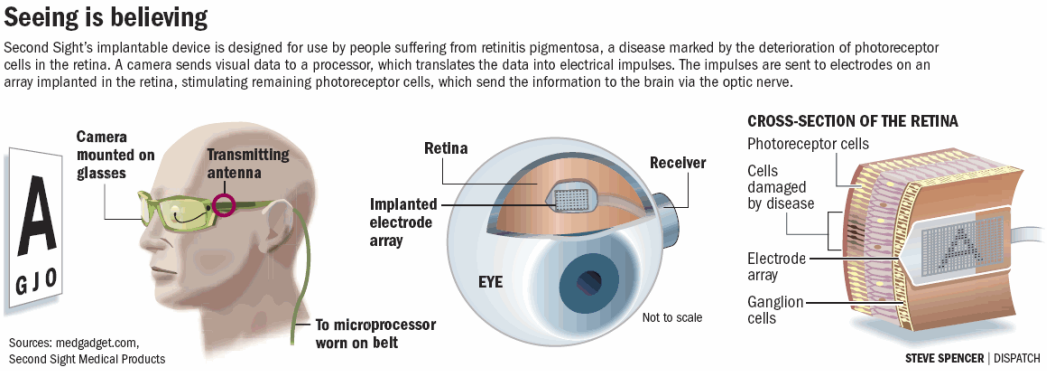

Fig.4.The design of the visual prosthesis ARGUS II[3]

Another solution, proposed by a Japanese team [28] are neural cell cultures done on MEMS (Microelectromechanical Systems), which, with guidance materials for axonal growth (or peripheral nervous tissue (e.g. peripheral nervous tissue graft or microtubes containing Swann cells and matrix extracellular), get to interconnect with the optic nerve or directly with the central nervous system, thereby serving as bioconductors. Since this hybrid implant does not require neural elements (bipolar cells, ganglion cells or optic nerve fibres) to be intact, the study has a target audience better than other products for diseases that cause blindness.

Conclusions

Although the eye and the optic pathway have been studied for more than 400 years, there are still many aspects of the functioning of the visual apparatus that require clarification; eloquent for this statement are the newly discovered functions of some retinal cells, which led to the delimitation of subpopulations within the already known retinal cell types. The mechanism for generating images was and still is intensively studied, but the structure and functioning of the retina and the transmission pathways or cortical areas where perception and analysis are done are yet incompletely explored, discoveries made in recent years showing that this domain is still developing.

However, it is gratifying that, without having a complete picture of its "modus operandi", researchers managed to produce equipment used to substitute, at least partially, the eye and today we are one step closer to realizing a "bionic eye" capable to restore vision to the blind. Due to the miniaturization of electronic chips and the increase in their processing power, the development of wireless communications, there are currently available more than one "artificial retina" devices which were successfully tested on humans. They offer, for now, only a partial recovery, limited vision and are indicated only in some eye diseases, which usually do not affect the neural pathways and cortical projection areas for vision, but the results are promising. And this is only the beginning.

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