Prosthetic Retinas Literature Review

Abstract

Retinal implants have become a more feasible eye-corrective tool in recent years. Examples of modern retinal implants include: the Argus II electronic epiretinal device, and the IMS electronic subretinal device (Jalil, Mills, & Stanga, 2017). Some more examples include, the Intelligent Retinal Implant system II (IRIS II) which has gained a CE mark[1], and the EPI-RET3 Retinal Implant System which is an entirely intraocular implant. (Bloch, 2019). In addition, the use of retinal implants has now become both economically advantageous as well as approved for public use as in 2011 the Argus II Retinal Prothesis system received a CE mark (Jalil, Mills, & Stanga, 2017). In 2013 it was approved by the FDA (Jalil, Mills, & Stanga, 2017). According to an economic evaluation on the cost effectiveness of the Argus II retinal prothesis on patients with retinitis pigmentosa, patients are now willing to pay for the cost of the implants within countries in the Eurozone (Borgonovi et al.,2014). Unfortunately, while the retinal devices do improve vision, they do not provide a "high enough resolution or acuity for a patient to regain a fully functional life" (Jalil, Mills, & Stanga, 2017). Some studies use a sub-retinal approach using a semi-conductor-based prosthetic to stimulate the retina electrically (Chow et al., 2001). However, this study employed the use of felines as test subjects, not human subjects. Other studies that have used near infrared radiation to stimulate retinal cells as visible light is not powerful enough to create adequate stimulation (Hierzenberger et al., 1999). Additionally, there have been methods which attempt to resolve blindness employing electrical stimulation of the retina using an epiretinal electrode array and conclude that microelectrode arrays can stimulate human retinas invoking visual perceptions in blind patients (Bornfeld et al., 2012). Overall, there has been a plethora of different methods over the past few decades used to stimulate the retinas in order to improve or enable vision in patients with poor or no eyesight. In more recent years, it has been demonstrated that not only are retinal implants safe for use in humans, but they are also economically viable for most patients.

Introduction

Visual System: Proper eye function is highly dependent on the eye's ability to metabolize and process light energy from the environment and transmit that energy in the form of action potentials through specialized nerve cells. These action potentials are then sent via the optic nerve directly into the brain. (Craig N. et al., 2019). The cornea, iris, crystalline lens, and ciliary body all play a part in focusing light on to the retina (Craig N. et al., 2019). The physiological process is as follows: light enters the eye through the cornea, which is the "glass window" to the eye (National Keratoconus Foundation, 2020). The cornea then bends the light using its refractive properties so that the light may pass through the pupil within the center of the retina. (National Keratoconus Foundation, 2020). The iris acts as a sort of camera shutter to the eye as it expands or contracts depending on how much light is present in the eye. After light rays pass through the iris, they enter the crystalline lens, which lengthens or shortens its width to focus light properly (National Keratoconus, Foundation, 2020). To be more specific, photoreceptor cells send signals through bipolar cells to Retinal Ganglion Cells (RGC's) inside the deepest regions of the retina and are then sent to the optic nerve into the brain (Craig N. et al., 2019). Within the brain, the signals travel partially through the optic chiasm and then onward into the lateral geniculate nucleus (LGN), and finally into the primary visual cortex where visual input is processed (Hon-Vu, and Duong, 2017).

Retinas: The retina is known as the sensory component of the eye (Craig N. et al., 2019). In the average human eye, light rays reach a focal point at the retina (National Keratoconus Foundation, 2020). The purpose of the retina is to convert light into light impulses which are transferred through millions of nerve endings which send the impulses to the optic nerve (NKF, 2020). The retina is made up of two different kinds of photoreceptive cells: rods and cones. Rods are more suitable for low light vision and are more prominent than cones in the eye. Cones are more suitable for color vision in areas with a greater abundance of light. Cones also have a tendency of being faster acting in terms of response times (Craig N. et al., 2019).

Commonplace diseases and conditions of the retina may include retinal tears, retinal detachments, diabetic retinopathy, epiretinal membranes, macular holes, macular degeneration, and retinitis pigmentosa (Mayo Clinic Staff, 2018). Retinal tears occur when the vitreous of the eye shrinks and pulls on the retina to rip. Typical symptoms usually include flashing lights and floaters[2] (Mayo Clinic Staff, 2018). Retinal detachments are indicated by a presence of liquid beneath the retina. Generally, this medical condition follows a retinal tear when the retinal tissue separates completely from its adjacent tissues (Mayo Clinic Staff, 2018). Diabetic retinopathy is as its name suggests, a condition which is caused by diabetes and results in deterioration of the capillaries in a patient's eye. This in turn causes fluid to leak underneath the retina causing it to swell, distorting the vision of the patient and potentially causing bleeding in the capillaries (Mayo Clinic Staff, 2018). Epiretinal membranes are scars which form on the surface of the retina which distort vision by tugging at its surface (Mayo Clinic Staff, 2018). Macular holes are created when there is excess friction between the retina and the vitreous. This results in a hole in the macula at the center of the retina. This condition can also be caused by eye damage (Mayo Clinic Staff, 2018). Macular Holes generally result in blurs or distortions in the central vision of patients. Generally, this condition affects patients over the age of 60 (National Eye Institute, 2019). Retinitis Pigmentosa is a rare genetic disorder which results in a degradation of the patient's retinal cells (National Eye Institute, 2019). Early symptoms may include loss of night-time vision and peripheral vision loss which can eventually exacerbate into complete loss of vision (National Eye Institute, 2019). Macular degeneration is the deterioration of the macula within the retina. Generally, this results in blurred or blind spots in the center of a patient's visual field (Mayo Clinic Staff, 2018). Patients with these disorders could greatly benefit from further development of retinal prosthetics. If research into retinal prosthetics were advanced further, then it could be argued that many of these disorders would become a thing of the past.

Retinal implants: Retinal implants are prosthetics which serve as replacements for dysfunctional retinas. Artificial retinas use a small camera which is mounted on a patient's pair of eyeglasses. Information received from this camera is then sent wirelessly to a microprocessor typically worn on the patient's belt. Data received by this microprocessor is then converted into an electronic signal which is then sent to a receiver on the patient's eye. The receiver then sends a signal to an array through a small cable causing it to create electrical pulses. These pulses ignore retinal cells that are no longer viable and are sent directly to the remaining viable retinal cells. These pulses eventually are transmitted through the optic nerve and then into the occipital lobe of the brain as they would in a normally functioning human being (U.S. Department of

Energy Office of Science, 2018). Currently, there are two prosthetics which show promise in improving the visual quality of life in humans. These include the Argus II electronic epiretinal device, and the Alpha-IMS electronic subretinal device (Jalil, Mills, and Stanga, 2017). Unfortunately, while these retinal devices do improve vision, they do not provide a sound enough resolution to recover fully functional vision (Jalil, Mills, & Stanga, 2017). Additionally, there have been attempts to stimulate the retinas electrically using a conductor-based prosthetic, but the efficacy of these devices is unclear as they have only tested on felines (Chow et al., 2001).

Specific Aim: The goal of this investigation is to act as a literature review for the current state of retinal prosthetics. The other objective is to inform the reader concerning the current state of retinal prosthetics in addition to potential innovations concerning the subject in the near future.

Review of Literature

As stated earlier, there are currently a handful of retinal prosthetics available to the public. These include the Argus II Electronic Epiretinal Device and the Alpha-IMS electronic subretinal device (Jalil, Mills, and Stanga, 2017). Fully functional vision is not possible with these devices however (Jalil, Mills, and Stanga, 2017). Most eye prosthetics appear to require an external device to process information captured by a camera. The Argus II Electronic Epiretinal Device is similar as it utilizes a pair of glasses with a camera mounted in the center and a coil that is located externally on the side arm of the glasses. This coil then connects to a portable video-processing unit that transmits electronic pulses to a 60-channel electrode chip which is implanted epiretinally (Brennan, 2018). The key to bridging the gap between natural and artificial vision seems to lie in enhancing image processing algorithms and improvements in data transferring devices as well as nanofabrication and conductive polymerization techniques (Bloch, 2019).

A remarkably interesting and promising aspect of newer retinal prosthetics is that some are designed to be completely intraocular. The EPI-RET3 is composed of a receiver coil and chip which is positioned in a aphakic capsular bag in addition to a retinal stimulating device which is connected directly to an epiretinal stimulation array (Bloch, 2019). Due to its design, the EPI-RET3 no longer necessitates a physical transscleral cable instead using inductive links to provide the implant with energy or data resulting in fewer eye infections and eye erosions (Bloch, 2019). Large stimulation artifacts are also reduced due to the EPI-RET3's ability to send ultrahigh frequency-pulse-charge controlled stimulation. This feature enables the device to stimulate bidirectionally in addition to allowing for recordings with microelectrodes (Bloch, 2019).

Another more innovative retinal prosthetic is the Intelligent Retinal Implant System II (IRIS II). The Iris II is remarkably similar to the Argus II Electronic Epiretinal Device but differs in a few key aspects. First, unlike the Argus II Epiretinal Device, the IRIS II uses a neuromorphic image device which reacts to visual input continuously and delivers coordinates for changing pixels and their respective light intensity levels. Information ascertained from these events is then separated into transient and sustained elements, which are then managed using powerful algorithms to enhance the overall video quality perceived by the subject (Bloch, 2019). This aspect of the device is designed to imitate the natural temporal resolution processes which healthy retinas are able to perform in addition to removing redundant visual input perceived by the potential patient (Bloch, 2019).

In addition to all of the epiretinal prosthesis there are also a certain number of post retinal prosthesis. The key difference is that epiretinal prostheses are implanted in the internal surface of the retina whereas post retinal prostheses are implanted under the retina between the choroid and the sclera (Humayun and Weiland, 2014). Some examples of post retinal prosthesis include the Boston Retinal prosthesis, the Artificial Silicon Retina, the alpha IMS and AMS, and the photovoltaic retinal implant (Bloch, 2019).

The Alpha IMS subretinal device consists of a microchip which is 3x3 mm^2 and uses 1500 electrodes which is the greatest number in any human prosthetic (Vision Research Staff, 2020). Patients that used the device were able to recognize human faces in addition to the ability to read door signs intelligibly (Vision Research Staff, 2020).

The Boston retinal prosthesis, as stated earlier, is a post-retinal implant (Chen et al., 2011). The prosthetic is a diminutive, airtight wireless device which was originally developed for use in Yucatan mini-pigs (Chen et al., 2011). The prosthetic was inserted on the exterior of the eye in orbit collecting energy and information from exterior sources wirelessly (Chen et al., 2011).

The artificial silicon retina is an ocular prosthetic which consists of a silicon chip which is 2 mm and with a thickness of .001 inches (McQuaid, 2002). The device also contains 3500 microphotodiodes[5] which are used to change light energy from photos to electrical impulses which are then sent to the remaining functional retinas in the potential patient’s eye (McQuaid, 2002). This conversion of light energy to electrical impulses mimics the natural function of normal healthy human retinas and is similar to many of the other retinal prosthetic devices mentioned. Patients with Age related macular degeneration and retinitis pigmentosa are the primary target populations this device attempts to treat (McQuaid, 2002).

Review of Methods

The Argus II Retinal Prosthesis required a phase II multicenter trial for safety which utilized 30 patients for evaluation on various visual tasks and real-world performance in the field (Bloch, 2019). The Iris II retinal implant required clinical trials for 10 patients over the course of 6 months which examined abilities such as square localization, direction of motion, image recognition, in addition to testing the patient’s visual fields (Bloch, 2019). As discussed earlier, the EPI-RET 3 is an entirely intraocular prosthetic meaning it requires no external parts to operate. The device required a clinical trial using a 25-electrode design which was then implanted into six patients. The prosthetic was removed after 4 weeks (Bloch, 2019).

The Boston Retinal Prosthesis used a slim film array of ejected deposited iridium oxide which would stimulate electrodes (Chen et al., 2011). The device also included an airtight titanium case comprising a 16 channeled stimulator chip in addition to discrete circuit elements (Chen et al., 2011). The sealed case was also attached to a secondary power source through a series of feedthroughs (Chen et al., 2011). Energy from these power sources was transported via a 500KHz carrier while frequency shift keying was used for data delivery (Chen et al., 2011). An external computer system was required for wirelessly programming the stimulation pulse strength, interval, and frequency (Chen et al., 2011). Electrode impedances were assessed through an analog to digital converter which tested output voltage waveforms all using an outbound telemetry channel (Chen et al,. 2011). The final assemblage of the device was examined within physiological saline both in vitro and in vivo inside two of the Yucatan mini-pigs for a maximum of three months examining stimulus artifacts created by the current drivers of the prosthetic (Chen et al., 2011).

The artificial silicon retina's efficacy has been examined in lab animals (McQuaid, 2002). Specifically, responses to light stimuli with brainwave electrical signals and retinal signals have been measured in said animals (McQuaid, 2002).

Results

After the phase II multicenter trials were completed for the Argus II Retinal Prosthesis, it was revealed that most patients were more adept with visual prowess, square localization, and direction of movement examinations with the prosthetic than without (Bloch, 2019). A study conducted over a 5 year period indicated that visual acuity, visual orientation, and visual mobility tasks improved over time (Bloch, 2019). Overall testing in the Iris II retinal implant yielded an improvement in the patient's visual field, image recognition, square localization, and direction of motion (Bloch, 2019). The amount of serious adverse effects (SAE's) was found to be .4 per patient (Bloch, 2019). The longevity of the Iris II device's functionality seemed to be somewhat lacking however and more improvements will be required both for the device and its surgical implementation before it can be marketable (Bloch, 2019). All of the patients who used the EPI-RET 3 indicated the perception of phosphenes[4] with small threshold stimulations commensurate with regions in the retina that had been stimulated. The appearance of these phosphenes diverged greatly from patient to patient (Bloch, 2019). Concerning the artificial silicon retina testing results, the induction of biological signals indicated that visual responses were achieved (McQuaid, 2002).

Discussion

With all of the recent advancements made in the field retinal implants, there appears to be great promise for the future in the field of ophthalmology. Hopefully as retinal prosthetics advance, there will be a greater shift towards intraocular prosthetics as this is a fundamentally more convenient design for patients. It is far simpler for a patient to have a one-piece implant located exclusively in the area of need in the body than it is to have an entire assembly of devices located all around the body. Many of the improvements made in more recent retinal prosthetics involve using advanced algorithms to produce more images with greater definition than before, while also focusing on removing redundant visual input. A clearer image is the first step of many towards granting patients full visual functionality. Perhaps someday with further research into cone receptors, patients will regain color vision as well.

Definitions

CE Mark[1]: CE (Conformitè Europëenne) Which is a French word for European conformity, is the EU’s (European Union) marking system established in 1985, for all products vended within the European Economic Area (EEA) (ASQ staff, 2020).

Floaters[2]: Tiny specks or blotches in vision which can be black or gray and can resemble cobwebs or strings that tend to move out of the field of vision when attempts are made to look upon them (Mayo Clinic Staff, 2019).

Aphakic[3]: Pertaining to the affliction known as aphakia or a person with a removed eye lens (Merriam Webster staff, 2020).

Phosphenes[4]: A perceived light spot created from pressure exerted on the eyeball or from any direct non light induced stimulus of the visual system (Lexico Staff, 2020).

Microphotodiodes[5]: These are defined as microscopic solar cells consisting of stimulating electrodes (McQuaid, 2002).

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