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Subretinal implantation of semiconductor-based photodiodes: Progress and challenges

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Abstract —

Retinal diseases that result in photoreceptor degeneration may spare the inner retinal layers. This review concerns a prosthetic approach to restoring visual function through the use of a semiconductor-based microphotodiode array implant, designed to be placed under the neural retina in the subretinal space. The fundamental idea is that current generated by the device in response to light stimulation will alter the membrane potential of overlying neurons and thereby activate the visual system. Initial acute studies indicated that the implant will function in the subretinal space in the absence of an external power supply. More recent and ongoing studies involve chronic subretinal implantations in normal animals. Post-operative studies have

demonstrated that implant function will persist for many months. These chronic studies have also assessed the biocompatibility of the implant. Photoreceptors are lost directly overlying the implant, due to the blockade of choroidal circulation to the outer retina by the solid disk device. In comparison, the inner retina maintains its characteristic lamellar structure. Away from the implant site, the retina retains normal anatomy and function. Future studies are needed to determine whether the implant can establish a functional connection to the inner retina and to determine the quality of this connection.

Key words: age-related macular degeneration, blindness, microphotodiode, retina prosthesis, retinitis pigmentosa, semiconductor.

INTRODUCTION

Retinitis pigmentosa (RP) and age-related macular degeneration (ARMD) are progressive blinding disorders of the outer retina. While the clinical course of RP and ARMD differ, both involve a degeneration of the photoreceptor cells (1-3), ultimately rendering the visual system insensitive to light. Although there is no proven effective therapeutic remedy for these disorders, a number of experimental strategies are being evaluated for their potential to slow or halt the disease time course. For example, disease progression has been slowed in experimental models of RP following intravitreal injection of certain growth factors (4). In addition, the identification of specific gene mutations has led to the development of gene therapy approaches that have proven useful in an animal model of RP (5). While both of these avenues are promising for treating patients early in the course of the degenerative process, they will be of relatively modest value for patients in whom the photoreceptors have already degenerated. To address this situation, other groups have explored the possibility that transplantation of retinal cells will restore vision to a blinded retina (6). In these studies, transplants have been composed of neuronal cells, retinal pigment epithelium (RPE) cells, or a combination of these cell types. The safety of the approach is supported by a large body of animal studies (6), as well as more recent investigations involving human subjects (7). With respect to efficacy, it is clear that cell transplantation can be effective at rescuing photoreceptors from degeneration (6). While it is likely that anatomical rescue will have a functional correlate, restoration of visual function following cellular transplantation has yet to be reported (6,8), but is an active area of endeavor.

An alternative approach toward functional restoration of the visual system following photoreceptor degeneration involves the application of external electrical stimuli. It is well established that visual sensations or "phosphenes" can be evoked by electrical stimulation at different levels of the visual pathway. For example, phosphenes are evoked by stimulation of the eyeball (9-14) or visual cortex (15-19). It is possible, by recording from sites over the visual cortex, to obtain an electrophysiological correlate of this sensation (20,21). Finally, *in vitro* and *in vivo* studies demonstrate that electrical potentials may be evoked by electrical stimulation of the outer retina (22-24).

It is important to note that qualitatively similar results are found in retinas with photoreceptor

degeneration. For example, visual phosphenes are induced in RP patients when current is passed across the eyeball (25). More recently, phosphenes have been induced during intraoperative sessions in which electrical current was applied directly to the retinal surface (26). In animal models, electrical stimulation has been found to evoke reproducible cortical potentials (21,27,28).

Because the remaining retinal layers are anatomically spared in RP and ARMD (1-3), these observations have led to attempts to electrically activate the visual system prosthetically. As diagrammed in **Figure 1**, two general approaches have been developed to address the possibility that a retinal prosthetic may be suitable for permanent implantation in affected patients. The "epiretinal" approach involves a semiconductor-based device placed in contact with the nerve fiber layer comprised of ganglion cell axons (29,30). This concept has been supported in acute intraoperative sessions in which electrical stimulation of the retinal surface induced visual phosphenes in patients with RP (26) and cortical potentials in animal models (21,28). Because similar results are obtained when prototype implant-type electrodes are used (31), emphasis is currently placed on the development of techniques to communicate the output of sensing devices to the implant electrodes (29). More recently, the surgical techniques required to stabilize prototype devices have been established (32).

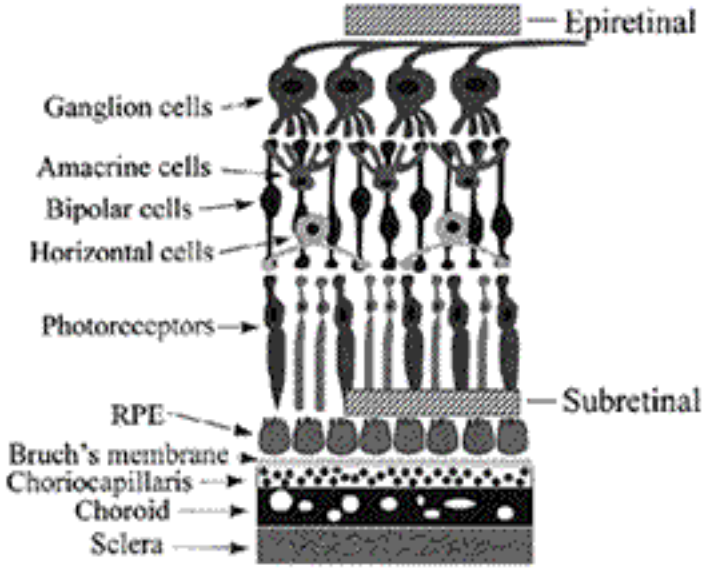

Figure 1. Schematic diagram of retinal cell layers. The relative locations of the epiretinal and subretinal approaches are indicated.

Since the late 1980s, we[1] have been exploring an alternative approach centered around the implantation of a semiconductor-based microphotodiode array disk into the subretinal space (33-38). The basic idea underlying this subretinal approach is that the implant may be used to artificially alter the membrane potential of neurons in the outer retina or remnants of this structure and thereby activate the visual system. Because the implant is designed to stimulate the retina at an early stage of the visual system, this approach would theoretically allow the normal processing networks of the retina to transmit this signal centrally. In the following, we review the progress that has been made regarding the subretinal approach and to identify future research directions.

METHODS

Implant Design and Fabrication

During the course of our work, many different prototypes have been designed and fabricated (33-38). Earlier devices were essentially a single photosensitive pixel, approximately 3 mm in diameter. The current microphotodiode array (MPA) is comprised of a regular array of individual photodiode subunits, each approximately 20×20-μm square and separated by 10-μm channel stops (37). The resulting microphotodiode density is approximately 1,100/m^2. This implant design has been adopted by another group pursuing the subretinal approach (39,40). Across the different generations examined, the implants have decreased in thickness, from ~250 μm for the earlier devices, to approximately 50 μm for the devices that are currently being used. Because implants are designed to be powered solely by incident light, there are no connections to an external power supply or other device. In their final form, devices generate current in response to a wavelength range of 500 to 1100 nm.

Implants are comprised of a doped and ion-implanted silicon substrate disk to produce a PiN (positive-intrinsic-negative) junction. Fabrication begins with a 7.6-cm diameter semiconductor grade N-type silicon wafer. For the MPA device, a photomask is used to ion-implant shallow P+ doped wells into the front surface of the wafer, separated by channel stops in a pattern of individual microphotodiodes. An intrinsic layer automatically forms at the boundary between the P+-doped wells and the N-type substrate of the wafer. The back of the wafer is then ion-implanted to produce a N+ surface. Thereafter, an insulating layer of silicon nitrate is deposited on the front of the wafer, covering the entire surface except for the well openings. A thin adhesion layer, of chromium or titanium, is then deposited over the P+ and N+ layers. A transparent electrode layer of gold, iridium/iridium oxide, or platinum, is deposited on the front well side, and on the back ground side. In its simplest form, the photodiode and electrode layers are the same size. However, the current density available at each individual microphotodiode subunit can be increased by increasing the photodiode collector to electrode area ratio.

Implant finishing involves several steps. Smaller square devices are produced by diamond sawing, affixed to a spindle using optical pitch, ground, and then polished to produce the final round devices for implantation. The diameter of these devices has ranged from 2-3 mm (for implantation into the rabbit or cat subretinal space) to ~0.8 mm (for implantation into the smaller eye of the rat).

Animal Models and Surgical Procedures

Initially, all implants were placed in the subretinal space of normal rabbits and cats; these species were chosen because their large eyes facilitated the surgery involved and because there is a vast literature surrounding the rabbit and cat visual system. Specific features of the vitreoretinal surgical procedures differed between these two animal models, and are described in detail elsewhere (24,37). The post-operative studies carried out on implanted rabbits and cats were designed to address two key issues surrounding the development of a retinal prosthetic: implant function in the subretinal environment and implant biocompatibility for the retina. More recent

studies, conducted here and elsewhere (39,40), have utilized a rat model. Although the smaller rat eye complicates the surgical procedures, a striking advantage of the rat is the availability of models with photoreceptor degeneration, due either to a defect in the RPE of the Royal College of Surgeons (RCS) rat (41) or to the expression of a mutant rhodopsin transgene (42).

Implant Function in Subretinal Space

Following the surgical procedures and post-operative recovery period, isolation of the electrical response of the implant was attempted by using infrared (IR) stimuli centered at 940 nm, to which the implant is far more sensitive than the native retina. Implant responses are recorded at the corneal surface, using a contact lens electrode. **Figure 2** presents representative responses recorded from three different cats a few months after surgery. In each case, illumination of an IR LED (upper trace) induces a negative polarity response recorded clearly at the corneal surface; at stimulus offset, there is a smaller response of opposite polarity. The differences between these responses reflect the materials used for the electrode layer. The responses of gold- and platinum-based devices are similar in amplitude and waveform. In both cases, the response returns to the baseline within a few ms of stimulus onset. In comparison, the response of the iridium/iridium oxide-based device has a substantial dc-component, so that the response persists for a longer period of time during the stimulus presentation and after-stimulus offset.

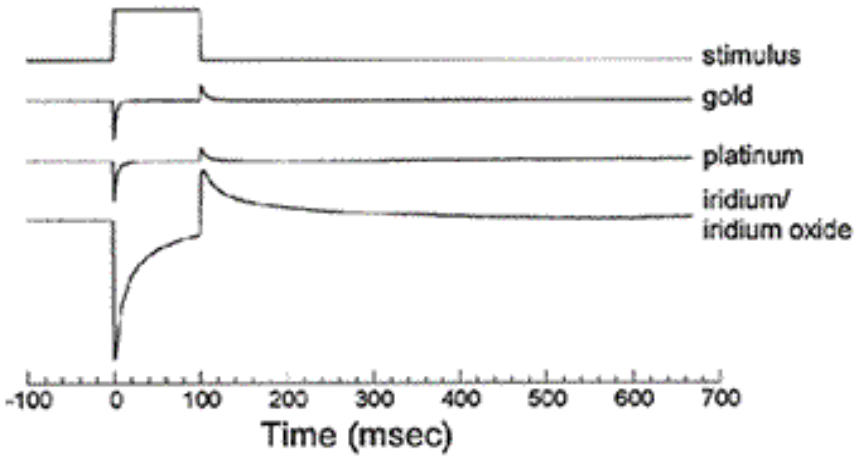

Figure 2. Electrical activity of subretinal implants. Upper trace, labeled 'stimulus', indicates the 100-msec period during which an IR LED was illuminated, and 50 µV vertically. Lower traces were recorded from the corneal surface of three cats with subretinal implants, several months post-operatively. Implants differed in electrode material, as indicated by labels at right.

We have used these types of recordings to examine the durability of the implant within the subretinal space. The responses of gold-based devices remain stable for several months post-operatively. Over time, however, the amplitude of the implant response declines steadily, due to dissolution of the gold electrode layer[1]. In comparison, responses of platinum- and iridium-based devices remain relatively stable during a similar duration of post-operative analysis, indicating that these materials may be less susceptible to deterioration in the subretinal environment. We have yet to explant the devices for closer inspection.

Biocompatibility

Implant biocompatibility is examined using a battery of assays (37,40). Throughout the post-operative period, implanted rabbit and cat eyes are examined by both indirect ophthalmoscopy and fundus photography. Aside from changes associated with the surgical procedures, there is no evidence of any progressive change in retinal appearance that might be associated with retinal toxicity. This impression is supported by measures of overall retinal function, made using the electroretinogram (ERG). In response to a white ganzfeld stimulus, responses of implanted eyes are similar in waveform to those of unoperated fellow eyes, but are slightly smaller in amplitude. The amplitude results are consistent with an overall reduction of ERG generators, due to the implantation surgery, and retention of normal function at retinal areas away from the implant.

At the end of the post-operative period, eyes are fixed for light microscopy. Consistent with the ERG results, retinal locations away from the implant site retain a normal architecture (37,40,43). In comparison, the retina directly overlying the implant shows a near complete loss of the photoreceptor cell layer with the exception of a thin layer of photoreceptor cell bodies (37,40). This loss is likely due to the solid disk implant blocking the diffusion of oxygen and other nutrients to the photoreceptors from the choroidal circulation. At the level of the inner retina, there are distinct differences noted between the animal models that have been used. While inner retinal layers are well-preserved in the cat (43) and rat (40), there are substantial changes in the rabbit (37). This difference is not surprising, since both cat and rat possess a well-developed inner retinal circulation which is virtually absent in the rabbit. Given the importance of this issue, we plan to restrict our future studies to animal models which possess, like human, a dual retinal circulation.

CONCLUSION

There are a number of important issues to consider regarding the possibility that a semiconductor-based photodiode implant may serve as the basis for a visual prosthesis for patients with RP, ARMD, and other retinal disorders that result in photoreceptor dysfunction yet spare the inner retinal layers. In the course of the work reviewed above, it has been possible to address several of these (37,40,43). It is now well established that a silicon disk implant will maintain a stable position in the subretinal space for an extended period of time. This result is a critical feature for a device intended to replace photoreceptor function within a limited retinal area. It is also clear that the implant will function electrically in the absence of any external power supply save incident light. Materials that are more resistant to the subretinal environment have been identified, and it may be possible to optimize implant durability further. In addition, charge-balancing by producing a biphasic balanced output may render the electrode layers more stable over extended periods of time and may improve biocompatibility.

The current generation of implants appears to have good biocompatibility for the neural retina. Aside from the changes in the outer retinal layers directly overlying the implant, the retina adjacent to the implant site and elsewhere retains a normal histological architecture, a normal ophthalmoscopic appearance throughout the postoperative period, and normal function on ERG

recordings to white-flash stimulation. Taken together, these results indicate that the implant is not detrimental to retinal areas away from the implant site. This biocompatibility is anticipated, given that all of the materials used to fabricate the subretinal implant are used in other types of medical implants (chromium has been eliminated in the recent generations of devices). Although photoreceptors are lost overlying the implant, this may not be of major concern because the device is intended for application to disorders in which the photoreceptors have already been injured. On the other hand, it is important to note that inner retinal layers overlying the implant appear generally spared in both cat and rat models. The status of the inner retina is obviously a critical question for the subretinal implant. To more completely define this, cytochemical markers that identify the localization and levels of cell-specific proteins are being brought to bear (40,43), as are other techniques such as single cell or multi-unit recordings (40). In addition, we are currently evaluating implants designed to improve nutrient flow from the choroid to the retina, due either to fenestrations made within the solid disk or to the use of prearranged individual microphotodiodes embedded within a permeable matrix.

A key question that remains concerns whether the subretinal implant will functionally interface with the neural retina and thus provide a means of artificially activating the visual system. It has been reported that IR stimulation will induce cortical potentials (VEPs) from implanted cats (44,45) and rabbits (40). Although this result would appear to provide evidence that the implant has made a functional connection to the neural retina, more recent studies indicate that these VEPs represent, at least partially if not wholly, an unappreciated sensitivity of the normal retina to IR wavelengths, a possibility currently being examined more closely. With respect to the question at hand, it is thus difficult to assign significance to VEPs recorded from implanted animals to IR light. A key reason concerns the choice of animal model. The use of normal animals makes it difficult to discriminate unequivocally implant-related retinal activity from normal visual function to IR stimulation. In the future, this key question may be more readily addressed by using animal models of RP, in whom a wider range of stimulus conditions and techniques can be brought to bear.

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[1]Chow AY, Pardue MT, Chow VY, Perlman JI, Peachey NS. Implantation of semiconductor-based photodiodes into the cat subretinal space. Unpublished manuscript.
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