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Subretinal implantation of semiconductor-based photodiodes: Durability of novel implant designs

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Abstract—Selective degeneration of the retinal photoreceptor layers underlies blindness in retinitis pigmentosa (RP) and other inherited retinal disorders. Because there are no therapies for these patients, we are evaluating the possibility that electrical stimulation delivered to the subretinal space by a microphotodiode array (MPA) could replace, in some aspect, the function of diseased photoreceptors. Early MPA prototypes utilized gold as the electrode material, which gradually dissolved during the postoperative period following subretinal implantation. Here we present the results obtained when different MPA materials were used. Semiconductor-based silicon MPAs (2 mm in diameter; 50 μm in thickness), incorporating iridium/iridium oxide (IrOx) or platinum (Pt) electrodes, were implanted into the subretinal space of the right eye of normal cats with the use of vitreoretinal surgical techniques. Indirect ophthalmoscopy, fundus photography, ganzfeld electroretinography, and histology were used for the evaluation of the implanted retinas postoperatively. Infrared (IR) stimulation was used to isolate electrical responses generated by the MPA. The unimplanted left eyes were used for control purposes. After the implantation surgery, subretinal MPAs retained a stable position in the subretinal space. Up to 12 months after surgery, there was little change in the magnitude of the electrical response of IrOx- and Pt-based MPAs to a standard IR light stimulus. Overlying the implant, there was a near-complete loss of the outer retinal layer, which is likely to reflect obstruction of choroidal nourishment to these layers by the solid disk implant. In addition, the inner retinal layers showed variable disorganization. Away from the implant, the retina displayed a normal appearance. In comparison to electroretinograms (ERGs) obtained from unimplanted eyes, responses recorded from implanted eyes had a normal waveform but were slightly smaller in amplitude. These results indicate that IrOx and Pt improve implant electrode durability and that implants incorporating these materials into the electrode layer do not induce panretinal abnormalities.

Key words: *biocompatibility, microphotodiode, prosthetic, retinitis pigmentosa, vitreoretinal surgery.*

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INTRODUCTION

Photoreceptor degeneration is known to occur in retinal disorders such as retinitis pigmentosa (RP) [1,2] and age-related macular degeneration (AMD) [3]. The absence of effective therapeutic remedies for these disorders has motivated the development of experimental strategies to restore some degree of visual function to affected patients [4,5]. Because the remaining retinal layers are anatomically spared, several approaches have been designed to artificially activate this residual retina and thereby the visual system. The possibility that the retina may be activated electrically has received support from a number of studies [6]. At present, two general strategies have been pursued to address the possibility that a retinal prosthetic may be suitable for permanent implantation into affected patients. The "epiretinal" approach involves a semiconductor-based device placed above the retina, close to or in contact with the nerve fiber layer, and is an active focus of a number of research groups [7–9]. The "subretinal" approach involves the electrical stimulation of the inner retina from the subretinal space by implantation of a semiconductor-based microphotodiode array (MPA) into this location [6,10,11].

The fundamental concept of the subretinal approach is that electrical charge generated by the MPA in response to a light stimulus may be used to artificially alter the membrane potential of neurons in the remaining retinal layers in a manner to produce formed images. This approach would theoretically allow the remaining intact retinal circuits of the inner retina to process this signal in a near-normal fashion and transmit this signal to the brain. In addition, the sampling density of a subretinal device could be designed to match that of the remaining photoreceptor or bipolar cell matrix, thereby providing a potentially high-resolution input to the retina.

While initial evaluation of subretinal prototypes used a rabbit model [12], more recent work has involved normal cats [6], which like humans possess a dual retinal circulation and therefore are more useful animal models with which to evaluate issues relating to the biocompatibility and durability of subretinal implants. Previously, we reported [6] that the subretinal MPA has good overall biocompatibility for the retina away from the implant (although outer retinal changes occurred at the implant site). However, the MPA design used in that study was not sufficiently durable for long-term application. In particular, dissolution of the gold electrode layer was observed, rendering the MPA only partially functional within ~6 months postimplantation. In addition, the original MPA design used chromium as an adhesion layer between the gold electrode layer and the silicon layers of the semiconductor. Exposure of this layer following dissolution of the overlying gold layer had the potential to expose the retina to chromium ions that may be neurotoxic. New electrode and adhesion materials have been incorporated into the MPA design so that these issues could be addressed. Here we describe several studies that examine the biocompatibility and durability of MPA prototypes based on these new designs.

MATERIALS AND METHODS

MPA Fabrication

Standard thin-film fabrication techniques were used to fashion MPAs, as described previously [6], except that activated iridium oxide (IrOx) [13] or platinum (Pt) was used for the electrode layers and titanium was used as the adhesion layer. The final MPAs were 50 μm in thickness and ~2 mm in diameter. MPAs had no external connections and were powered solely by incident light. Because the MPA responds to a wavelength range of 500 nm to 1100 nm, near infrared (IR) stimuli may be used to activate the electrical response of the implant in relative isolation [14]. The implant design consisted of a regular array of individual photodiode subunits, each approximately 20 μm × 20 μm square and separated on all sides by 10–μm channel stops. MPA fabrication began with a 3-inch diameter semiconductor grade N-type silicon wafer. Shallow P+-doped wells, separated by channel stops, were ion-implanted into the front surface of the wafer with the use of a photomask. An intrinsic layer automatically formed at the boundary between the P+-doped wells and the N-type wafer substrate, and the back of the wafer was then ion-implanted to produce a N+ surface. A thin adhesion layer of titanium was deposited over the P+ and N+ layers followed by deposition of individual transparent IrOx or Pt electrodes on the front active side and a common electrode of the same material on the back ground side. Changing the photodiode collector-to-electrode area ratio can control the current density available at each individual photodiode. In the format used here, the photodiode and electrode

layers are the same size. Smaller square MPAs (3 mm × 3 mm) were produced by diamond sawing. Optical pitch then was used to affix the square MPAs to a spindle, which was ground and then polished to produce the final round implant.

Animals and Surgical Procedures

Normal adult cats, maintained on a 12:12, light:dark cycle, were used in this study. All procedures were approved by the local Animal Care and Use Committees and were in accordance with the Association for Research in Vision and Ophthalmology's Statement for the Use of Animals in Ophthalmic and Vision Research.

Cats were initially sedated with intramuscular ketamine HCl (11 mg/kg) and xylazine HCl (2.2 mg/kg), intubated and subsequently ventilated with 0.9 percent halothane in 100 percent O_2. A temporal incision exposed the frontal process of the zygomatic bone, and a portion of the bone was removed so that the temporal sclera could be accessed. The eye was then rotated with a traction suture and the *area centralis* was viewed with an operating microscope. A 3-mm long sclerotomy was made ~7 mm posterior and parallel to the temporal limbus. This location lies over neural retina, but was chosen to allow access to the vitreous chamber behind the relatively large cat lens. A localized separation of the retina was created at the posterior pole. This was done with injection of a small amount of balanced salt solution into the subretinal space. A retinotomy was then created near the edge of this saline bleb. A partial vitrectomy was made between the scleral incision and the retinotomy, and a channel was formed with viscoelastic (Healon, Pharmacia, Inc.) through which the MPA could be manipulated. After the MPA was inserted through the retinotomy into the subretinal space, it was gently moved closer to the *area centralis*. The incisions were closed and local antibiotic was applied. All implantations were made in the right eye; the left eye served as an unoperated control.

Electrophysiology

Cats were sedated with intramuscular ketamine HCl (11 mg/kg) and xylazine HCl (2.2 mg/kg), and the pupils were dilated with 1 percent mydriacyl and 2.5 percent phenylephrine HCl. Retinal potentials were recorded with the use of an electroretinogram- (ERG-) jet corneal contact lens electrode coated with 1 percent methylcellulose and referenced to a Grass cup electrode (Grass Instruments, Inc.) placed in the mouth; a needle electrode placed subcutaneously on the trunk served as the ground.

The electrical response generated by the MPA was recorded from the corneal surface to stimuli generated with an IR light-emitting diode (LED) (λ_{max} = 935 nm; bandwidth at 50 percent = 50 nm) driven by a function generator. Stimuli were 100 ms in duration and were presented at 2 Hz. In each trial, the responses to 400 successive stimulus presentations were differentially amplified (0.5–1500.0 Hz), averaged, and stored on an LKC UTAS E-2000 signal averaging system. LED intensity was 15 mW/Sr, as measured with a radiometer equipped with an IR sensitive attachment (Model IL 1800, International Light, Inc.). In each recording session, 5 to 10 trials were obtained. After the implant responses obtained in each trial were measured individually, these values were averaged together. The first such recording session was made 1 month following implantation. These recording sessions were then repeated at monthly intervals during the initial postoperative period and at 2- to 3-month intervals thereafter. The purpose of these measurements was for the evaluation of the stability of the implant response during the postoperative period. All the results obtained from a given animal were normalized to the value obtained in the recording session in which the largest average response was obtained. This was done so that the potential effect of individual differences in the amplitude of the recorded implant response could be minimized.

In a final recording session, conventional full-field flash ERGs were recorded from both the implanted eye and the fellow control eye to white light. After a 2-hour period of dark adaptation, animals were prepared as described above, except that the recordings were made simultaneously from the implanted and unimplanted eyes with a pair of ERG-jet contact lens electrodes. Full-field strobe flash stimuli (t < 1 ms) were presented either in the dark or superimposed on a rod-desensitizing adapting field (1.3 log cd/m^2). ERGs were first recorded to stimuli presented to the dark-adapted eyes. Intensity-response functions were generated with flash intensity that ranged from –3.0 to 1.0 log cd s/m^2. In different trials, strobe flash stimuli were presented in order of increasing intensities. In each trial, at least two successive responses were averaged. After a 10-min period of light adaptation, responses were recorded to stimuli ranging from –0.1 to 1.2 log cd s/m^2. In each trial, responses to 25 successive

flashes presented at a rate of 2.1 Hz were averaged. At the completion of these recordings, which were made after 6 to 11 months of postoperative follow-up, the implanted retina was examined histologically (see "Histology" paragraph for description).

The amplitude of the dark-adapted ERG a-wave was measured from the baseline to the a-wave trough. The amplitude of the dark- and light-adapted b-wave was measured from the trough of the a-wave to the b-wave peak or, if no a-wave was present, from the baseline to the b-wave peak.

The purpose of the ERG measurements was to compare responses recorded from implanted eyes with those obtained from the unimplanted fellow eye. All the ERG a- and b-wave measurements made from a given animal were normalized to the maximum b-wave amplitude obtained from the unimplanted control eye. This was done so that individual differences in overall ERG amplitude could be minimized, which could obscure this comparison.

Indirect Ophthalmoscopy and Fundus Photography

At the beginning of each recording session, after anesthesia induction, the MPA and retina were evaluated by indirect ophthalmoscopy. In addition, fundus photographs were taken at ~2-month intervals. These were taken with a Kowa small animal hand-held fundus camera.

Histology

Eyes were enucleated under deep anesthesia; after which, animals were then immediately sacrificed. The anterior portion of the eye was removed, and the eyecup was immersion fixed in 2.5 percent glutaraldehyde, 2 percent paraformaldehyde phosphate-buffered saline solution. After overnight fixation, the eyecup was rinsed in phosphate buffer and the MPA was gently removed from the subretinal space. Pieces of the eyecup were embedded in epoxy-resin (Embed 812, Electron Microscopy Services, Inc.), sectioned with a diamond knife, and stained with toluidine blue for light microscopy.

RESULTS

Figure 1 presents fundus photographs taken from cats several months following implantation of either an IrOx-based (left) or a Pt-based MPA (right) in the subretinal space. The pigmentary changes located near the MPA are a typical feature and are associated with the surgical implantation procedure [6]. Aside from these changes, the retina retains a relatively normal appearance following implantation with either device, in agreement with our prior experience with previous MPA designs [6].

Figure 2(a) illustrates how the electrical responses of the MPA were measured. The upper tracing indicates the 100-ms time course over which a 935-nm IR LED was activated. The lower tracing shows a representative recording obtained from the corneal surface in an implanted animal. At IR stimulus onset, a large amplitude negative spike is seen, representing the electrical activity of the MPA itself. At stimulus offset, a spike of opposite polarity is also seen, which was always smaller in amplitude than the onset spike. The open arrows indicate that the magnitude of the implant response was measured from the prestimulus baseline to the peak of the initial negative spike. The large amplitude implant spike masked any potential response of the native retina.

This electrical response was used to evaluate MPA durability. Specifically, recordings were made at specific postoperative time points from each implanted animal with a standard IR stimulus. **Figure 2(b)** plots the amplitude of the negative electrical spike as a function of time through the postoperative period. Data points indicate the average (± SD [standard deviation]) across animals implanted with IrOx- (●) or Pt-based (○) MPAs, as well as for gold-based devices reported previously [6]. Prior to averaging, the amplitudes measured for each cat were normalized to the maximum response recorded for that animal. This procedure reduced intersubject variability and facilitated comparison of results concerning the durability of different implant designs. In comparison to electrical responses generated by gold-based devices, which rose gradually to a maximum before declining [6], responses of IrOx- and Pt-based MPAs were substantially more stable throughout the 1-year postoperative period. These results indicate that IrOx- and Pt-based MPAs retain a stable electrical response to IR light for a longer period of time than do devices incorporating gold as the electrode material.

Full-field ERGs were used to assess the overall status of the implanted retina. **Figure 3(a)** presents a series of ERG responses recorded under dark-adapted

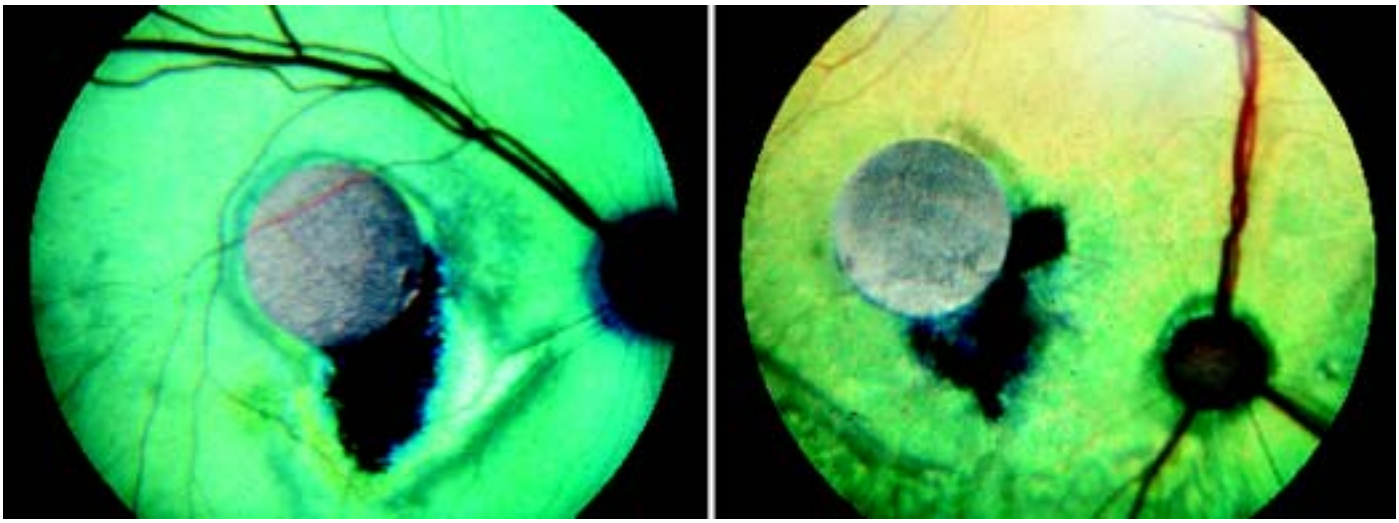

Figure 1.
Fundus photographs of cats with either an IrOx-based (left) or Pt-based MPA (right) implanted in the subretinal space, both taken after more than 6 months of implantation.

conditions from the implanted and unimplanted control eyes of a representative cat with an IrOx MPA. Throughout the intensity range examined, it is apparent that the waveforms of the responses obtained from the implanted eye were similar to those recorded from the control eye. The overall amplitude of ERG responses was, however, slightly smaller in the im-planted eye. **Figure 3(b)** presents intensity-response functions for the dark-adapted ERG a- and b-waves. Data points indicate the average (± SD) response obtained across eight cats implanted with an IrOx-based MPA (●) and five cats implanted with a Pt-based device (○). In this figure, all of the amplitudes recorded from a given animal were normalized to the largest b-wave amplitude obtained from the unimplanted eye. This procedure minimizes interanimal amplitude variability and allows a clearer examination of the difference between implanted and control eyes. Compared to the control eye, there is a modest reduction in the ERG response of the implanted eyes. A repeated measure two-way analysis of variance (ANOVA) indicated that this reduction was statistically significant for the dark-adapted b-waves and for the cone ERGs recorded from cats with IrOx- or Pt-based MPAs (all $P < 0.05$). There was no significant difference in a-wave amplitude between implanted and unimplanted eyes ($P > 0.05$), which may reflect the reduced number of stimulus intensities at which an a-wave is obtained. The magnitude of this reduction was similar for IrOx- and Pt-based MPAs. Compared to the control eye (♦), the amplitude of the ERG b-wave obtained from the implanted eye averaged 93.1 percent for the dark-adapted response and 83.9 percent for the cone ERG. Similar reductions were noted previously for gold-based or inactive devices [6], and these may reflect the area of the implant as well as retinal injury associated with the vitreoretinal surgical procedures.

The implanted retina was also examined anatomically, in five IrOx-implanted and three Pt-implanted animals**. Figure 4** presents cross sections of the retina from two cats implanted for 8 months with either an **(a)** IrOx or **(b)** Pt MPA. In all cats, there was a near-complete loss of the photoreceptors inner and outer segments overlying the MPA. There was variability across animals in the number of photoreceptor cell bodies preserved. In two out of eight retinas, photoreceptor cell bodies remained to form a thin outer nuclear layer (ONL) even after 8 months of implantation (**Figure 4(a)**). In six other cats, the ONL layer was not distinguishable from the inner nuclear layer (INL), and only a few photoreceptor cell bodies were present (**Figure 4(b)**). The inner retinal layers were better preserved, although some areas appeared partially disorganized. In five out of eight implanted retinas, the INL was thinner near the middle of the implant area. The reason for this is unknown but may be due to the

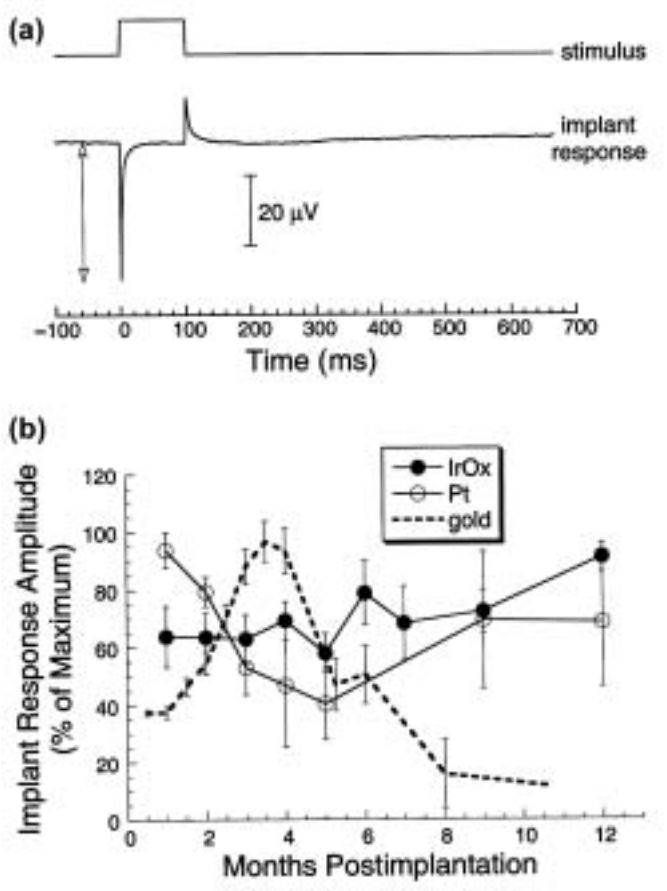

Figure 2.
(a) How electrical response of MPA was measured. Upper trace, labeled "stimulus," indicates 100-ms illumination of an IR LED. Lower tracing indicates that amplitudes were measured from prestimulus baseline to initial negative peak. **(b)** Amplitude of initial negative implant spike plotted as a function of time following implantation surgery. Results obtained from each cat were normalized to value obtained in recording session in which largest average response was obtained. At each postoperative time point, data points indicate average (± SD) value obtained across all cats implanted with an IrOx-based (●) or Pt-based (○) MPA. As some animals were used for histological studies, number of cats tested varied across the different postoperative time points. For IrOx-based MPAs, nine cats were tested from 1–4 months postoperative, seven were tested at 5 months, five tested at 6–7 months, three were tested at 8 months, six were tested at 10 months, and two were tested at 12 months postimplantation. For Pt-based MPAs, seven cats were tested from 1–3 months postoperative, six were tested at 4–5 months, and two were tested at 6–12 months. Dashed lines indicate average results obtained with gold-based MPAs [6].

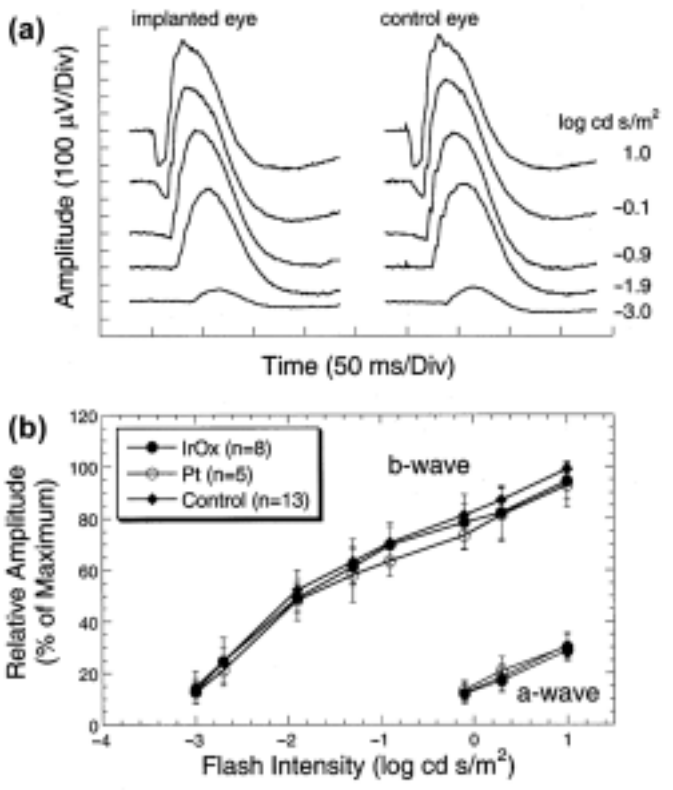

Figure 3.
Electroretinography. **(a)** Intensity series of ERGs obtained from two eyes of a representative cat with an IrOx-based MPA. **(b)** Intensity-response functions for dark-adapted ERG a- and b-waves recorded from unimplanted control eyes (♦) and eyes implanted with IrOx-based (●) or Pt-based (○) MPAs. For each cat, response amplitudes were normalized before averaging to maximum b-wave response recorded from unimplanted eye. Each data point indicates average (± SD) of all cats studied.

central implantation area being furthest from the choroidal blood supply. In agreement with our prior analysis of implanted cat retinas [6], we did not observe a fibrotic or gliotic capsule surrounding the implant area in any of the eight retinas examined, although this impression may reflect the methods used to remove the implant after fixation. To address this possibility, we since have developed a technique to section the retina without removing the implant.

There were no observable differences between retinas implanted with either the IrOx or Pt devices, and the present observations are in general agreement with our previous studies of implanted cat retinas [6]. Because the present study concentrated on long-term implantations, the time course over which these changes develop is not known. At the edge of the implant, the retina takes on a normal appearance (**Figure 4**); in some retinas, the ONL at the edge is seen to curve outward, giving the impression

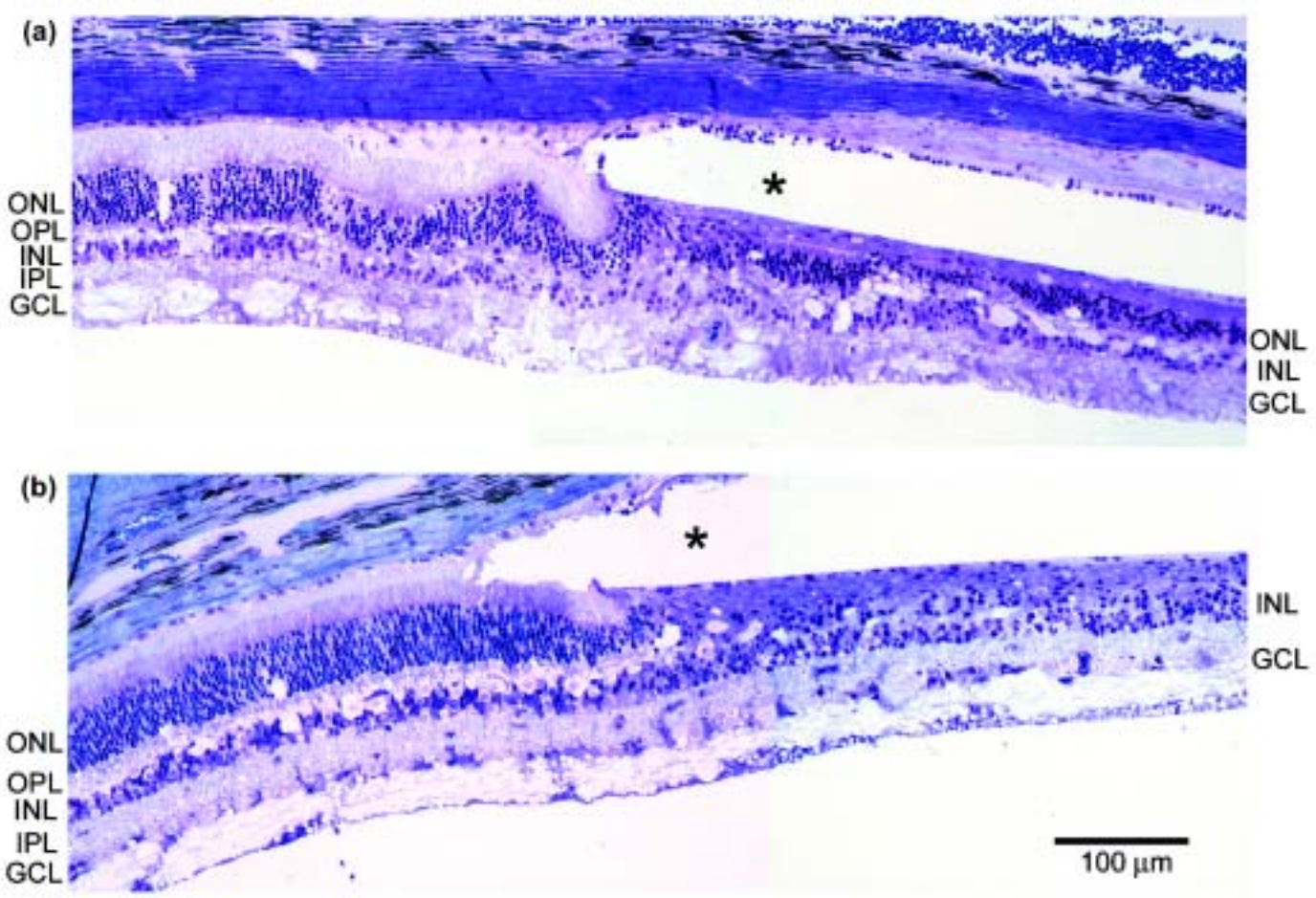

Figure 4.
Retinal cross section made at site of implantation of an **(a)** IrOx or **(b)** Pt MPA. Implant site is designated by *. Overlying the device was a near-complete loss of photoreceptor layers, while inner retinal layers were better preserved. Retinal areas adjacent to implant maintained a relatively normal appearance with intact photoreceptors and outer nuclear layer (ONL = outer nuclear layer, OPL = outer plexiform layer, INL = inner nuclear layer, IPL = inner plexiform layer, GCL = ganglion cell layer).

that the implant may have pushed against the retina during implantation. No changes in retinal architecture were noted beyond the implant edge in any of the animals examined.

DISCUSSION

The present investigation studied a number of issues that may impact on the possibility that a semiconductor-based MPA implant may serve as the basis for a visual prosthesis for patients with RP, AMD, and other retinal disorders that result in photoreceptor dysfunction yet spare the inner retinal layers. The present generation of MPAs was found to maintain a stable level of electrical function for an extended period of time following implantation into the subretinal space. While the response amplitude of gold-based MPAs gradually decreased over time, thought to be due to dissolution of the gold electrode layer [6], a similar decline was not observed for either IrOx- or Pt-based devices. This observation indicates that these electrode materials may be more suitable than gold for implant designs.

The present results indicate that these subretinal implants are generally biocompatible with the mammalian retina outside the area of implantation. The retina had near-normal function on ERG recordings to white-flash stimulation. Away from the implant and surgical sites, the retina retained a normal ophthalmoscopic appearance throughout the postoperative period and retained a normal histological architecture.

While the implant did not appear to be detrimental to retinal locations some distance from the implant site, the retina overlying the device showed substantial alterations. Directly above the implant, there was a near-complete loss of outer nuclear layer cells (**Figure 4**). An explanation for this loss would be that these outer retinal changes might be caused by the MPA blocking the choroidal circulation to the photoreceptors, which depend on the choroid for oxygenation [15], and disrupting communication with the retinal pigment epithelium. These changes are unlikely to be caused by MPA electrical activity, since similar outer retinal changes were observed in cats with inactive MPAs [6]. However, the loss of photoreceptors overlying the MPA may not be of critical consequence because the device is intended for application to disorders in which photoreceptors have been lost. For example, in the Royal College of Surgeons (RCS) rat, no significant differences were noted between retina overlying and adjacent to IrOx-based MPAs [16]. Although the inner retinal layers of implanted cats were better preserved, areas of disorganization were observed. To better define the status of the inner retinal layers, we have carried out immunocytochemical studies. As reported elsewhere [17], the neurochemical organization of the inner retina is altered in the retina overlying the implant. However, these changes are likely to reflect the loss of photoreceptors induced by the implant, since similar changes were observed in the Abyssinian cat [17], a naturally occurring feline model of photoreceptor degeneration.

The present results indicate that either IrOx- or Pt-based subretinal implants have a greater durability than gold devices when placed in the subretinal space. These materials appear to be appropriate choices for further development of retinal prosthetics for use in the subretinal space and perhaps in other areas. Although this is an important step for the continued development of the MPA approach to a retinal prosthetic, the present results do not allow us to address other important questions. For example, from these data, we cannot determine if the MPA initiates activity within the visual system in implanted cats. It is also not possible to extrapolate the amplitude of the field potentials generated by the electrical response of the implant to the magnitude of currents generated within the retina. As a consequence, we do not know how close this current is to that required to activate the retina from the subretinal space [18]. Although cortical responses can be recorded from MPA-implanted cats in response to IR stimulation [19], interpretation of these responses is complicated by the sensitivity of the native retina to these stimulus wavelengths [14] and, as a result, do not provide unequivocal evidence of implant-mediated retinal activity. As a consequence, evaluation of the possibility that the MPA will make a functional connection with the visual system will require further studies conducted with different animal models and/or preparations.

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