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OPTICAL COCHLEAR IMPLANTS: EVALUATION OF SURGICAL APPROACH AND LASER PARAMETERS IN CATS

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Abstract

Previous research has shown that neural stimulation with infrared radiation (IR) is spatially selective and illustrated the potential of IR in stimulating auditory neurons. The present work demonstrates the application of a miniaturized pulsed IR stimulator for chronic implantation in cats, quantifies its efficacy, and short-term safety in stimulating auditory neurons. IR stimulation of the neurons was achieved using an optical fiber inserted through a cochleostomy drilled in the basal turn of the cat cochlea and was characterized by measuring compound action potentials (CAPs). Neurons were stimulated with IR at various pulse durations, radiant exposures, and pulse repetition rates. Pulse durations as short as 50 μ s were successful in evoking CAPs in normal as well as deafened cochleae. Continual stimulation was provided at 200 pulses per second, at 200 mW per pulse, and 100 μ s pulse duration. Stable CAP amplitudes were observed for up to ten hours of continual IR stimulation. Combined with histological data, the results suggest that pulsed IR stimulation does not lead to detectable acute tissue damage and validate the stimulation parameters that can be used in future chronic implants based on pulsed IR.

Keywords

Deafness; cochlear implants; laser radiation; optical stimulation; infrared neural stimulation; neural prostheses; hearing loss

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INTRODUCTION

Contemporary neural prostheses use electrical current that directly stimulates neural tissue to replace or assist nervous system function lost during injury or disease. Among neural prostheses, cochlear implants are considered the most successful devices, restoring some hearing in severe-to-profound deaf individuals. Cochlear implants (CI) take advantage of the tonotopic organization of the cochlea. CIs encode acoustical information derived from high-frequency sounds into electrical pulse trains that are delivered in the base and low-frequency signals in the apex of the cochlea (Kiang et al., 1972; Kiang et al., 1965; Rose et al., 1967). Thus, by discrete stimulation of a particular location along the length of the cochlea, the devices attempt to mimic the natural sound encoding in the auditory pathway. Contemporary implants use up to 22 intracochlear electrode contacts delivering electrical pulses to the cochlear nerve. Although users can discriminate stimuli on multiple electrodes, clinical and psychophysical studies have shown that implant users do not achieve functional performance on all channels (Eddington et al., 1978; Eddington, 1983; Townshend and White, 1987; Fishman et al., 1997; Dorman et al., 1998; Friesen et al., 2001). For cochlear implant users, the channel interactions due to spread of current in tissue limits the speech recognition scores to a maximum of about seven to ten electrode contacts. Results indicate that CI electrodes often activate broadly overlapping neural populations and in some cases inappropriate cochlear locations (Black et al., 1983; Robillard et al., 1979). Controlling the spread of activation and selectively stimulating a smaller portion of the auditory neurons could improve the performance of CI users.

Towards this goal, a novel approach has been proposed: using pulsed infrared radiation (IR) at wavelengths near 1860 nm (1840–2120nm range) to stimulate auditory spiral ganglion cells (Izzo et al., 2006b). The use of pulsed infrared lasers may increase the spatial selectivity in neural stimulation (Rajguru, 2010a; Richter, 2010) and increase the number of independent channels. While the idea of exciting neurons with light is not novel (for review see Richter et al., 2009), the use of pulsed IR to selectively stimulate neurons has only recently been demonstrated in sciatic nerve and cochlear spiral ganglion cells (Izzo et al., 2006b; Wells et al., 2005). In previous studies, we have shown that the auditory nerve can be stimulated with a benchtop optical source. However, chronic stimulation has not been possible because of the large size of the stimulation source. Lockheed Martin Aculight has recently developed a small (4.5×4.5×1.7 cm, 35 g) infrared nerve stimulator (INS) for chronic implantation. The current device is a single channel source operating at a wavelength of 1850 nm that allows for stimulation of the cat auditory nerve.

In this study, we assessed the efficacy and short-term safety of this “optical cochlear implant” in normal hearing and acutely deafened cat cochleae. Before an implantable device can be translated into human prostheses, safety must be documented in an animal model. Also, the surgical approach for a long-term implantation of the device is described. Cochlear function was determined with optically evoked compound action potentials (CAP) recorded at the round window and the results demonstrate the effectiveness of pulsed IR in stimulating auditory neurons. Histological study of cochlear tissue following ten hours of continual IR stimulation did not reveal any damage assessed with light microscopy. The data presented here validates the IR parameters to be used in chronic safety studies, which are now feasible with such an implantable device.

MATERIALS AND METHODS

Five adult healthy cats of either sex were used in the experiments. Both ears of three of the cats were tested, whereas in the other two cats only one ear was tested. Procedures were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committee of Northwestern University.

Anesthesia and surgery

For premedication, the animals received an intramuscular injection of acepromazine (0.02 mg/kg), butorphanol (0.4 mg/kg), and atropine (0.05 mg/kg). An intravenous (i.v.) access was secured in a vein from the front leg. Anesthesia was induced by i.v. injection of ketamine (3 mg/kg) and diazepam (0.3 mg/kg). The animals were then intubated to allow ventilation. Anesthesia was maintained with isoflurane (1.5%–3%) using an anesthesia workstation (Hallowell EMC). Core body temperature was maintained at 38°C with a thermostatically controlled heating pad. Heart rate, respiration rate, body temperature and O₂-saturation were monitored continuously using a BioVet3 monitoring system. The animals received a continuous infusion of Ringer's Lactate solution with 2.5% dextrose at a rate of 10 ml/kg/h.

Surgical approach

To access the bulla, a C-shaped incision was made behind the ear. The outer ear canal was exposed and dissected close to the bony skull. Next, the head was secured in a rigid Stoelting stereotactic head holder. Access to the cochlea was gained by drilling a bullotomy of approximately 2×2 mm. A 125 µm silver wire was placed at the rim of the round window to measure compound action potentials (CAPs). After acoustically-evoked CAPs were recorded to confirm cochlear function in the normal hearing animals, a cochleostomy was drilled with a 0.5 mm Buckingham footplate hand drill (Richards Manufacturing Co., Memphis, TN) to access scala tympani. A 200 µm diameter optical fiber (Ocean Optics) was inserted through the cochleostomy into the scala tympani and allowed initial measurements of IR-evoked CAPs in normal hearing and acutely deafened animals with a benchtop laser. In one experiment, the optical fiber was placed at the round window and IR-evoked CAPs were recorded (data not shown).

The surgical implantation technique for the chronic infrared neural stimulator was investigated in three cats. A 200 µm optical fiber, which was fed through a glass cylinder (Figure 1A), was inserted through the cochleostomy into scala tympani. The optical fiber was oriented towards the spiral ganglion. The polished surface of the fiber was approximately 250–300 µm from the spiral ganglion. The remaining opening of the cochleostomy was filled with muscle tissue. The cylinder was pushed gently along the optical fiber until it contacted the outer cochlear wall. The cylinder rested on a metal holder, which was fixed to the lower edge of the bullotomy (Figure 1B). A counter metal piece was placed from the top edge of the bulla (Figure 1C) to fix the recording round window electrode and the glass cylinder in place. After the top section was fixed to the bulla using a 1 mm screw, the open sections were filled with dental acrylic. The implanted optical fiber was long enough to feed through the skin. The laser source was mounted to a pedestal on the cranium and could be removed when no stimulation was ongoing. The inserted optical fiber had a connector that allowed coupling to the output of the laser device (Figure 1D). Optically evoked responses were acutely recorded with the implantable stimulator (see below for details).

Acoustic measurements

Acoustically evoked CAPs were determined as described previously (Richter et al., 2008) before and after deafening. Briefly, voltage commands for the stimuli were generated using a computer I/O board (KPCI3110, Keithley, Cleveland, OH) and attenuated using a Weinschel corporation 8310 series attenuator. The output was used to drive a headphone speaker (Beyer, DT 770Pro). To measure an acoustically evoked CAP threshold curve, the stimuli were delivered at frequencies between 2–50 kHz with a resolution of 6 steps/octave. The acoustic stimuli were 12 ms tonebursts with 1 ms rise and fall times.

Once the IR-evoked CAPs were measured and the efficacy of laser stimulation was determined in a normal hearing animal, Neomycin (about 50 µl, 20mM dissolved in Ringer's lactate,

warmed to 38°C) was injected through the cochleostomy to acutely deafen the animals. Acoustically evoked responses were recorded post-injection to confirm deafness.

Optical measurements

Initial IR stimulation of the auditory nerve was achieved using a benchtop Capella pulsed near infrared laser (Lockheed-Martin Aculight). The Capella laser diode is tunable between 1850 to 1869 nm and was operated at 1860 nm, which was slightly different than the compact implantable stimulator (1850 nm). The small difference in wavelength changes the optical penetration of IR in water from 833 μm to 715 μm and hence should not affect the responses. The Capella laser is capable of delivering continuous trains of single pulses at repetition rates between 10 and 250 Hz. The output was coupled to a 200 μm diameter low-OH optical fiber (Ocean Optics) for transmission and delivery. The optical fiber was mounted to a micromanipulator (Narishige HMW103) and was inserted approximately 200 μm through the cochleostomy. Optically evoked CAPs were recorded for different radiant exposures (0 – 366 mJ/cm^2), pulse durations (50, 100, 150, 200 and 250 μs), and pulse repetition rates (10 – 250 Hz). CAP amplitudes were measured between the first negative peak (N1) and the following positive peak (P1). The threshold for optical stimulation was set at CAP amplitude of 20 μV . The approximate spot size at the bony wall of Rosenthal's canal is taken to be 200 μm in diameter. Responses to ten stimulus presentations were averaged for each measurement. Optically evoked responses were conducted in the normal hearing and acutely deafened cochleae.

The miniaturized laser source (referred to as INS in the text) used for long-duration stimulation studies, was designed by Lockheed Martin Aculight and measures 4.5×4.5×1.7 cm, weighs 35 g, and emits radiation at 1850 nm. This source was also integrated with an optical fiber with a core diameter of 200 μm . The variable parameters for this laser were: power (0 – 210mW), pulse duration (adjustable between 50–200 μs), and pulse repetition rate (adjustable between 200–400 Hz). The external battery provides stimulation for approximately 8 hours at maximum output level and repetition rate of the device.

Histology

At the end of one of the acute experiments, the right bulla was harvested from the skull for histology. The surrounding soft tissues were removed and the bulla was fixed in 4% paraformaldehyde in phosphate buffered saline (PBS, pH 7.4). The bone surrounding the cochlea required two weeks of decalcification in 1L of 4% formic acid combined with 2% sodium citrate in distilled water, changed every other day. It was followed by four days in 200ml RDO decalcifying agent (Apex Engineering, Plainfield, IL), changed daily. All solutions were kept at room temperature. Tissue was then dehydrated through graded ethanol in distilled water, 1×50%, 3×70%, 3×90%, 3×100% each for 30 min. followed by clearing in xylene. Tissues were placed in molten paraffin wax (Paraplast Xtra, Leica Microsystems, St. Louis, MO) for 30 min followed by two changes of the wax at 60 min intervals. Tissues were placed in fresh molten Paraplast Xtra and placed in tissue molds, then allowed to cool and solidify. The cochlea was oriented parallel to the base of the mold. The embedded cochlea was sectioned entirely at 10 μm sections.

Tissue sections were affixed to glass slides by overnight incubation at 58°C. Sections were rehydrated through three 10 min soaks in xylene, followed by 10 min each of 2×100% ethanol, 2×90% ethanol, 2×70% ethanol and 3 changes of distilled water. Masson Trichrome staining (Carson, 1997) of the tissue was performed. After staining, the tissue sections were dehydrated using the above procedure. At the end of the last xylene change, coverslips were affixed to slides using a standard toluene based slide mounting resin. Digital photomicrographs were taken using standard transmitted light microscopy.

RESULTS

Cat cochleae ($n=8$) from five cats were used to study the neural responses to IR stimulation. To monitor cochlear function, CAP threshold curves were recorded at the beginning and at different times during the experiment. Ten minutes following the injection of Neomycin through the cochleostomy, CAP thresholds were elevated on average by 15 dB below 6 kHz and were absent above 15 kHz. We could not acoustically evoke any CAPs 60 min. post-injection in deafened cochleae at any frequency. The deafening was similar to results described in other studies in gerbils (Richter et al., 2008), and cats (Hardie et al., 1999; Hartmann et al., 1990; Snyder et al., 1990; Wang et al., 2009).

To test the efficacy of IR nerve stimulation in cats, CAP were evoked with radiation pulses generated by the laser. We could successfully evoke CAPs in all animals, *pre- and post-deafening*, with the Capella as well as the miniaturized INS. Figure 2 shows CAP peak-to-peak amplitudes measured at various exposure levels for a 100 μ s pulse. The CAPs were averaged over 10 stimulus presentations. The neural responses to IR before and after deafening are shown for one example cochlea. The CAPs were primarily composed of one negative peak (N1) followed by a positive peak (P1). At lower energy levels, the positive peak was broader. No microphonics could be seen in the traces. The latency between the stimulus and the onset of the response at lower radiant exposures (below 0.02 J/cm²) was $\sim$ 2 ms and it reduced to 1 ms at higher exposure levels. The maximum CAP amplitudes measured 30 minutes to an hour post-deafening were reduced by nearly 50% (6 dB) and the threshold for stimulation was increased on average by 8 dB.

The evoked CAP amplitudes were measured as a function of the laser pulse duration for pulses between 50–250 μ s (Figure 3). Evoked CAP amplitudes before deafening (left column) and after deafening (right column) are plotted at different radiant exposures. The results from each of the cochleae are shown in Figures 3A–E. Figure 3F shows the averaged amplitudes. Post-deafening data were not recorded in the two cochleae that were used to develop the surgical approach. A sigmoidal increase in the CAP amplitudes can be observed with increasing radiant exposure for each case. CAPs were evoked in response to laser pulses as short as 50 μ s. A plateau in CAP amplitudes occurred at higher radiant exposures. This trend is seen for each cochlea, independent of the absolute CAP amplitudes. Input-output (I/O) curves for each of the pulse durations showed a similar trend i.e. an increase in CAP amplitudes in response to increasing radiant exposures, followed by a plateau. Post deafening, the maximum amplitude of evoked CAPs was smaller and the thresholds for stimulation increased for all pulse durations. For longer pulse durations, higher radiant exposures were required to elicit the same amplitude of CAPs and the trend was consistent before and after deafening. The results are consistent with our previous report in gerbil cochleae (see discussion, (Izzo et al., 2006b)).

The threshold for the optically evoked response was measured for different pulse durations. CAP amplitude for the threshold calculation was measured between the first negative peak and following positive peak, and set at 20 μ V (marked with dotted lines in Figure 3A). The radiant exposure thresholds, both before and after deafening, for a representative cochlea (Figure 3A) are summarized in Table 1. For comparison, the radiant exposure thresholds measured at the same 20 μ V level from the averaged responses (Figure 3F) are also included. Thresholds for averaged responses followed a similar trend as the individual cochleae. They increased post deafening by approximately 6 dB for the shortest pulse durations and up to 18 dB for the longest pulse durations. Differences in absolute amplitudes of the CAPs in each cochlea are likely caused by variations in the placement of the optical fiber or by the differences in the number of neurons recruited by the incident radiation. The maximum amplitudes of CAPs (N1 to P1) were also calculated for the representative cochlea (Figure 3A) and are presented in Table 2. The averaged amplitudes for the 5 cochleae followed a similar trend (mean $\pm$ S.D. in Table 2).

The amplitudes reduced post deafening by 10 dB (50 μ s) to 14 dB (250 μ s) and were significantly different when compared to pre-deafening (t-test).

Effect of pulse repetition rate

Compound action potential amplitudes were successfully evoked at different pulse repetition rates between 10 and 250 Hz (Figure 4). Measurements were conducted in normal and deafened cochleae. The data shown in Figure 4 follow the same arrangement of Figure 3 – the results from each of the cochlea are shown in Figures 4A–D and Figure 4E shows the averaged amplitudes. The pulse duration was kept constant at 100 μ s for each pulse repetition rate. The curves show a sigmoidal increase in CAP amplitude with increasing radiant exposures. The CAP amplitude plateaus at higher radiant exposures. The maximum amplitude of the CAPs that can be evoked with higher pulse repetition rates was smaller and amplitudes plateau quickly as compared to lower repetition rates. Deafening leads to a decrease in the maximum amplitude and an increase in thresholds for evoked CAPs.

The threshold radiant exposures for a 20 μ V peak-to-peak optically evoked CAP from the representative cochlea and averaged responses (Figure 4A, E) are presented in Table 3. Higher radiant exposures were required to evoke CAPs of the same amplitude, both before and after deafening. The CAP amplitudes did not reach the 20 μ V peak-to-peak value selected as the threshold for repetition rates greater than 150 Hz in some of the cochleae. The maximum amplitude of CAPs reduced post-deafening by 12–14 dB on an average (Table 4) and were significantly different compared to the amplitude pre-deafening (t-test).

Maximum CAP amplitudes evoked at higher pulse repetition rates were much smaller compared to CAP amplitudes obtained at lower repetition rates (Figure 5). The figure illustrates the change in CAP amplitude after the onset of stimulation for different pulse rates. As can be seen in Figure 5A, the amplitude of the first action potential after the onset of laser stimulation was similar across stimulation rates. The amplitudes of subsequent action potentials decreased for higher stimulation rates. Individual CAPs were sorted for various pulse rates from 10 Hz to 250 Hz and their amplitudes were plotted as a function of time (Figure 5B). Exponential curve fits using Wavemetrics Igor Pro (exponential function: $y=y_0+Ae^{\frac{-x}{\tau}}$) provided the time constants for decrease in CAP amplitudes which are shown in Figure 5C.

Continual stimulation

To quantify the safety of optical implants for stimulating the auditory neurons, IR evoked CAP amplitudes were recorded over long durations with the miniaturized INS device. One cochlea that was continually irradiated for 10 hours was histologically analyzed following the experiment. CAPs are sensitive markers for cochlear function and any cochlear damage should be reflected in a change in amplitude. The spiral ganglion cells were continually stimulated with the INS for durations of up to 10 hours. The IR wavelength was 1850 nm and the pulse repetition rate was 200 Hz. CAP amplitudes were recorded every 5 minutes at a radiant exposure of 3.18 mJ/cm². Figure 6 shows three examples for the measured CAPs. The cochleae were stimulated for 3, 8 and 10 hours respectively. There was no significant change in CAP amplitude over these durations while IR was stimulating the tissue. In fact, for the 8 hour study when the laser output was increased from 3.18 mJ/cm² to 41.34 mJ/cm², indicated by the arrow, there was a simultaneous increase in IR-evoked CAP amplitudes. During the 10-hour stimulation, acoustically evoked CAPs from the cochlea were recorded at approximately 1 and 6 hour time points (indicated by *). No CAP could be evoked by acoustic stimuli. IR-evoked CAPs remained stable to the end of the experiment. The overall shape of CAPs remained similar over time.

Histology of the cochlea

Histological sections of the cochlea that was stimulated continually for 10 hours were examined. Figure 7 shows photomicrographs of a cochlear section in the plane of the cochleostomy in the basal turn. The panel on the left shows the area of interest in a longitudinal section through the cat cochlea. The cochleostomy was ~500 μm in diameter. The dotted line indicates the approximate orientation of the optical fiber through the cochleostomy. The fiber was placed in the scala tympani and oriented towards the spiral ganglion cells. Panels a and b on the right show magnified views of the tectorial membrane and the spiral ganglion cells respectively. Cochlear cross-sections (a) revealed few sensory hair cells, which may explain the lack of acoustically evoked neural responses. On the other hand, the spiral ganglion cells showed little to no damage (b). This suggests that the IR stimulation did not cause any detectable tissue damage and the observations are consistent with our previous studies in gerbils.

DISCUSSION

We have shown in mice, gerbil, guinea pig and now a cat model that auditory neurons can be stimulated with pulsed infrared radiation. In the present study, we have validated short-term safety of a cochlear INS by measuring stable CAPs that were evoked with optical radiation in deafened cat cochleae. CAPs could be observed in deafened cochleae in response to laser stimulation at a wavelength of 1860 nm for the Capella benchtop laser over a wide range of parameters. The pulse durations at which CAPs were evoked range between 50–250 μs , and the pulse repetition rates were varied between 10–250 Hz. The CAPs remained stable during continual stimulation at 200 Hz for up to 10 hours with the implantable INS operating at 1850 nm. Moreover, we have established a surgical approach for the implantation of the chronic infrared neural stimulator in a cat model.

Each cochlea showed similar trends for various pulse durations as well as pulse repetition rates. The peak-to-peak CAP amplitude before deafening was near 150 μV for the shortest pulse durations (50 μs) and reduced to 130 μV for the longest pulse durations (250 μs). The same trend continues post deafening, although the maximum amplitude of CAPs reduced by 8 dB on an average and the thresholds for stimulation increased between 4–20 dB. Similar observations were made in our previous studies in gerbils and guinea pigs (Izzo et al., 2007b; Richter et al., 2008), although the thresholds post deafening in other species did not vary as much as they did in the cats. The input-output curves for shorter pulse durations peaked quickly, whereas the curves for longer durations rose with a much longer time constant suggesting that for pulse durations greater than 100 μs , larger radiant exposures are required to evoke the CAPs of same magnitudes. It is possible that the rise time of the optical pulse may be more significant in optical stimulation of the cochlea and not the total energy deposited in the tissue.

The data for the pulse repetition rates showed similar sigmoidal curves that saturated. At higher pulse repetition rates (above 100 Hz), an increase in the radiant exposures did not lead to a proportional increase in the CAP amplitudes. However, the radiant exposures required to cross a threshold CAP amplitude did not vary significantly with pulse repetition rates. For example, the thresholds for 20 μV CAPs before deafening were between 3–13 mJ/cm^2 – a range of 12 dB. After deafening, the thresholds increased on average by 7.76 mJ/cm^2 at pulse repetition rates below 150 Hz. At pulse repetition rates greater than 150 Hz, the CAP amplitudes did not reach the set threshold value in some of the cochleae. However, close examination of the CAPs showed that even at repetition rates of 250 Hz CAPs had clear N1/P1 peaks (Figure 5A).

Some single auditory neurons have maximum firing rates in the range of 300–400 Hz (Izzo et al., 2007b; Littlefield et al., 2008). In the current experiments, we were able to successfully stimulate cochlear neurons at a sustained rate of 250 Hz. There is a reduction in maximum

amplitudes of the CAPs at repetition rates greater than 50–70 Hz. This can be explained by reduced synchronization of responses from single fibers. We cannot verify single neuron entrainment from CAPs but the results clearly indicate that it is possible to stimulate auditory neurons with optical stimulation at rates up to 250 Hz. In addition, we have successfully recorded responses of single fibers to infrared radiation previously (Littlefield et al., 2008), which support our results.

The observation of stable CAPs for continual stimulation over 10 hours and post experiment histological evidence indicates that optical stimulation did not cause acute tissue damage affecting cochlear function. CAPs are a sensitive marker for physiological state of cochlear function. For example light cooling of the cochlea results immediately in corresponding changes of cochlear function (Ohlemiller et al., 1992; Ohlemiller et al., 1994). In case the optical IR stimulation does heat and damage neurons, the number of cells that are able to depolarize in response to the stimulus should decrease. In such a case, the peak-to-peak amplitude of the CAPs should decrease. However, in our study, the CAP amplitudes did not change even after 10 hours of continual stimulation at 200 Hz, giving evidence that no significant acute changes were induced in the spiral ganglion cells due to IR stimulation. The amplitude of optically evoked CAPs did reduce post-deafening, though the CAPs evoked at different pulse durations and repetition rates both before and after deafening are composed of clear N1/PI peaks (Figure 2). The reduction in CAP amplitude and the increase in CAP threshold is likely related to the number of spiral ganglion cells recruited by IR stimulation. There is evidence that Neomycin reduces the density of spiral ganglion cells (Richter et al., 2008). It is known that if the number of spiral ganglion cells decreases by a factor of three, the radiant exposure required to evoke same magnitude CAP increases by an order of magnitude.

Recent work (Rajguru, 2010b) has shown that IR stimulation can activate vestibular hair cells and evokes phase-locked responses up to 100 pulses per second. Similar responses likely exist for auditory hair cells. Although, we have previously collected data in chronically deafened animals, in cochleae without living hair cells and our results suggest that IR stimulates spiral ganglion cells.

The question regarding the mechanism behind IR stimulation of biological tissue remains unanswered. It has been hypothesized that a photothermal mechanism is a likely means depolarizing neurons via IR stimulation (Wells et al., 2007). One possible means for a photothermal mechanism to activate neurons is via thermally-gated ion channels, including the TRPV channels. It has been shown that the TRPV channels are activated by heat and subsets of TRPV ion channels are expressed in the dorsal root and trigeminal ganglia of rats (Caterina et al., 1997), as well as in cochlear structures of both the rat and guinea pig (Balaban et al., 2003; Takumida et al., 2005; Zheng et al., 2003). TRPV channels are members of the Transient Receptor Potential (TRP) superfamily and have gained increased attention due to their many and vast roles in sensory physiology. Another possibility is that IR leads to intracellular changes in Ca^{2+} concentration by depleting intracellular calcium stores. Helium-neon and/or near-infrared laser radiation has been suggested to lead to release of Ca^{2+} from intracellular stores into the cytoplasm (Olson et al., 1981), possibly evoked by heat acting on mitochondria and/or sarco-endoplasmic reticulum (Olson et al., 1981; Walker et al., 1985). Excitatory effects in the sciatic nerve, using the same type of IR pulse stimulation applied in the present study, were presumably due to the conversion of the radiation pulses into heat (Izzo et al., 2006a; Wells et al., 2005). Recent work (Tseeb et al., 2009) suggests that thermosensitive intracellular Ca^{2+} responses are sensitive to the sarco-endoplasmic reticulum Ca^{2+} ATPase inhibitor thapsigargin. Hence, it is likely that IR has a photothermal effect, similar to Helium-neon or near IR radiation on intracellular Ca^{2+} leading to the observed neural responses.

A major objective of this research is to develop a multi-channel optical cochlear implant for use in humans. Present report focuses on a single channel IR device. Future versions of an IR based neural stimulator will have to incorporate new laser technology and/or arrays of laser sources now available for designing a multi-channel implant. The design would benefit from a variable wavelength tunable laser source to accommodate differences in individual cochlear anatomy and any limitations with fiber placement. An optical fiber inserted through a cochleostomy could be contaminated with bone dust in some cases. The presence of a significant amount of bone in front of the optical fiber may limit the efficacy of IR in stimulating spiral ganglion cells because of diffraction and scattering of light. However, current implant techniques minimize such contamination and preserve residual hearing to a good extent. There will be growth of fibrous tissue surrounding the cochleostomy and in front of the optical fiber. Given the penetration depth of IR in fibrous tissue, it is not expected to significantly reduce the efficacy of the IR stimulation. Ongoing chronic experiments and post experiment histology will help us better understand potential problems. The surgical approach and device design will need to be modified if necessary.

The potential advantages of cochlear stimulation with IR relates to the selectivity of the stimulation (Izzo et al., 2007a; Izzo et al., 2008). This may lead to more channels recognized by implant users and hence improved performance of CI user. The advantages of IR stimulation will need to be further characterized and evaluated histologically. Present results suggest that optical stimulation of the cochlea is effective and safe over a short stimulation period. Experiments are now underway to test the safety of IR optical cochlear implant in chronic cat model.

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Figure 1.

Illustrates the placement of the “chronic” implant. (A) The optical fiber housing consisted of glass cannula that was covered by a biocompatible Teflon tube. The fiber was inserted approximately 500 μm inside the cochleostomy. (B) The arrow indicates the cochleostomy drilled in the basal turn of the cochlea. (C) The fiber and the round-window recording electrode (arrow) were held in place by two sterilized stainless steel plates attached to the bulla. (D) The entire assembly was secured by dental acrylic.

Figure 2.

Shown are typical examples for CAPs recorded from one cochlea before (left) and after (right) deafening with a 50 μl intracochlear injection of 20 mM neomycin in Ringer's lactate solution. The radiant exposure increases from the bottom trace to the top trace and is marked. We successfully evoked CAPs in all animals post-deafening although the peak-to-peak amplitudes reduced after deafening and the threshold for stimulation increased.

Figure 3.

Effect of pulse duration on the optically evoked CAPs was observed. The plots A–E show the responses observed from individual cochleae in response to IR pulses with different pulse durations both before and after deafening. The dotted lines in panel A indicate the threshold set at 20 μ V. The pulse durations are marked in the legend. The averaged CAP amplitudes are shown in panel F. The error bars indicate one standard deviation.

Figure 4.

Effect of pulse repetition rates on optically evoked CAPs. The plots A–D show CAP amplitudes evoked from four different cochleae. The pulse repetition rates were varied between 10 and 250 Hz and are marked in the legend. The averaged CAP amplitudes and one standard deviation are plotted in panel E.

Figure 5.

At higher pulse repetition rates, the reduction in synchronization of neural responses led to reduction in the CAP amplitudes. A) CAPs evoked in response to pulse repetition rates of 10–250 Hz are shown. B) The drop in CAP amplitudes from the time of stimulation onset was measured over a duration of 1 s. C) Exponential functions were fitted to CAP amplitudes and time constants were recorded.

Figure 6.

Short-term safety was evaluated by continual stimulation at 200 Hz. The CAP amplitudes recorded every 5 minutes from three cochleae are shown. The arrow indicates a time when the laser power was increased from 3.18 mJ/cm² to 41.34 mJ/cm² in one cochlear. A simultaneous increase in CAP amplitudes was observed. The CAP amplitudes remained stable over 10-hour of IR stimulation.

Figure 7.

Histological examination of the cochlea was carried out following 10 hours of continual IR stimulation at 200 Hz. A longitudinal section in the basal turn shows the cochleostomy and approximate orientation of the optical fiber. a) The close-up of the organ of Corti indicates that there were no remaining hair cells in the cochlea. b) Histological sections showed little or no loss of spiral ganglion cells, as seen in the close-up. Scale bars are indicated on each section.

TABLE 1CAP thresholds (mJ/cm²) for various pulse durations (μs)

	Representative cochlea (Figure 3A)		From the average (Figure 3F)	
Pulse duration	Before deafening	After deafening	Before deafening	After deafening
50	1.6	14.83	0.79	1.63
100	4.21	16.3	0.88	2.4
150	5.66	17.25	6.52	18.01
200	8.75	19.24	7.78	72.3
250	9.64	24.04	13.12	105.74

TABLE 2 Maximum CAP amplitudes (μV) for various pulse durations (μs)

Pulse duration	Representative cochlea (Figure 3A)		Mean $\pm$ S.D. (Figure 3F)	
	Before deafening	After deafening	Before deafening	After deafening
50	186.22	40.7	146 $\pm$ 62.18	45.19 $\pm$ 30.28
100	181.6	62.26	161.44 $\pm$ 90.9	45.22 $\pm$ 30.21
150	175.96	50.23	140.79 $\pm$ 62.62	25.65 $\pm$ 22
200	177.4	50.6	124.72 $\pm$ 55.06	29.68 $\pm$ 20.27
250	174.9	53.9	130.8 $\pm$ 48.62	27.51 $\pm$ 24

TABLE 3CAP thresholds (mJ/cm²) for various pulse repetitions (Hz)

Pulse rates	Representative cochlea (Figure 4A)		From the average (Figure 4E)	
	Before deafening	After deafening	Before deafening	After deafening
10	4.21	16.22	4.1	19.1
20	4.77	13.04	8.1	16.7
50	5.71	18.29	9.8	22.5
100	6.1	29.6	13.7	53.2
150	6.13	24.1	14.25	-
200	6.2	-	15.1	-
250	6.54	-	16.4	-

TABLE 4 Maximum CAP amplitudes (μV) for various pulse repetitions (Hz)

Pulse rates	Representative cochlea (Figure 4A)		Mean $\pm$ S.D. (Figure 4E)	
	Before deafening	After deafening	Before deafening	After deafening
10	150.2	46.33	166.81 $\pm$ 105.47	31.89 $\pm$ 20.41
20	142.52	42.66	124.27 $\pm$ 74.87	41.5 $\pm$ 18.55
50	110.66	37.72	85.65 $\pm$ 34.56	27.92 $\pm$ 13.85
100	76.54	22.2	67.99 $\pm$ 27.53	18.4 $\pm$ 5.4
150	63	22.59	53.89 $\pm$ 18.73	16.75 $\pm$ 8.2
200	51.4	17.39	45.49 $\pm$ 14.2	13.92 $\pm$ 4.92
250	42.1	15.56	41.83 $\pm$ 15.06	13.13 $\pm$ 3.44