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Abstract. The discovery that a pulsed laser could trigger an auditory neural response inspired ongoing research on cochlear implants activated by optical stimulus rather than by electrical current. However, most studies to date have used visible light (532 nm) or long-wavelength near-infrared (>1840 nm) and involved making a hole in the cochlea. This paper investigates the effect of optical parameters on the optically evoked compound action potentials (oCAPs) from the guinea pig cochlea, using a pulsed semiconductor near-infrared laser (980 nm) without making a hole in the cochlea. Synchronous trigger laser pulses were used to stimulate the cochlea, before and after deafening, upon varying the pulse duration (30–1000 μs) and an amount of radiant energy (0–53.2 mJ/cm^2). oCAPs were successfully recorded after deafening. The amplitude of the oCAPs increased as the infrared radiant energy was increased at a fixed 50 μs pulse duration, and decreased with a longer pulse duration at a fixed 37.1 mJ/cm^2 radiant energy. The latency of the oCAPs shortened with increasing radiant energy at a fixed pulse duration. With a higher stimulation rate, the amplitude of the oCAPs' amplitude decreased. [DOI: 10.1117/1.JBO.20.8.088004]

Keywords: near-infrared laser; cochlear implant; optical stimulation; optically evoked compound action potentials.

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1 Introduction

Cochlear implants based on electrical stimulation have helped to restore the hearing of over 220, 000 patients with severe sensorineural hearing loss.[1] However, some inherent limitations of electrical stimulation, such as stimulation artifacts,[2] the electrode interaction, and the damage to the neural tissue at the electrode–tissue interface caused by high current levels or by chemical reactions,[3–8] have perplexed thousands of researchers in this field. Recently, it has been demonstrated that a pulsed near-infrared laser can also stimulate the auditory nerve.[9]

In the early 1960s, Arvanitaki and Chalazonitis first quantified how nerve cells are affected by different wavelengths of radiation, ranging from visible light to near-infrared.[10] In 1971, Fork consistently stimulated molluscan neurons with a 480 nm laser, obtaining measurable nerve impulses without causing obvious damage or irreversible change to the neurons, which demonstrated the safety of optical stimulation.[11] Subsequently, by using modern two-photon techniques, Hirase et al. found that the excitation of pyramidal neurons from the mouse visual cortex was likely associated with the laser wavelength and radiation.[12] In 2005, Wells et al. used a pulsed low-energy infrared laser to stimulate rat sciatic nerves, confirming that optical energy from a pulsed laser can provide the free energy transition necessary to activate neural tissue, and that the interaction between optical radiation and tissue may be influenced by the characteristics of tissue water absorption.[13] Izzo et al. and Richter et al., from Northwestern University, first proved the feasibility of an optical cochlear implant in the mammalian cochlea. They used an optical fiber to replace the electrode and adopted a laser source instead of an electrical current source to stimulate spiral ganglion neurons in the cochlea. Indeed, the pulsed infrared laser evoked the activity of the auditory nerve, which has inspired efforts to further develop and improve the performance of optical cochlear implants.[9,14–20] To preserve and enhance the residual function of the cochlea, the research team led by Wenzel et al. used a 532-nm nanosecond pulsed laser to irradiate the basilar membrane and osseous spiral lamina of a guinea pig, successfully activating the cochlea without any apparent damage.[21,22]

Compared with electrical stimulation, using a laser to excite auditory neurons has several appealing traits such as no direct contact, high spatial resolution, and no stimulation artifacts;[2] therefore, laser stimulus appears to be ideal for cochlear implants.[23] Although many lasers with different wavelengths have been proved to be able to induce compound action potentials (CAPs) in the cochlear, it is needed to find the most effective wavelength, which could stimulate the spiral ganglion cells in Rosenthal's canal outside the cochlear most efficiently and safely.

Selecting a suitable laser for using in surgery relies on optimizing the absorption of light by tissue.[24] Light interacts with tissue in four key ways: transmission, reflection, scattering, and absorption.[25] Reflection mainly depends on the optical

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properties of the tissue and the irritant surrounding it and reflection does not depend strongly on wavelength, so it could be neglected when evaluating a laser wavelength for a surgical application.[24] To induce the compound action potentials outside the cochlear, the laser light needs to penetrate the round window and lymph in the cochlear to reach the spiral ganglion cells in the Rosenthal's canal. Therefore, the laser light intensity in the direction of propagation mainly depends on scattering and absorption. In general, the amount of scattering is inversely proportional to the wavelength of the laser. Shorter wavelengths undergo a large amount of scattering at the round window, while longer wavelength could lose a large amount of energy in the lymph due to the high absorption coefficient of water. An exception to this rule is laser light beyond the mid-infrared region of the electromagnetic spectrum.[26] However, to the best of our knowledge, studies using these wavelengths are few in number, comprising only a handful of experiments at the 808 nm wavelength.[27] There is also insufficient information on laser parameters. Therefore, we chose the wavelength of 980 nm which has not been previously explored for use in optical stimulation of the auditory nerve for our study. Furthermore, we could compare and contrast the power requirements among different wavelengths later and discuss the mechanism of optically induced compound action potential with other previous works.

The purpose of this work is to induce optically evoked compound action potentials (oCAPs) by applying a 980-nm laser stimulus outside the cochlea without impairing the cochlea. In addition, we examined the effects of laser pulse duration, laser power, and radiant exposure to identify optical parameters relevant to the further development of optical cochlear implants.

2 Materials and Methods

All measurements were made *in vivo* using adult guinea pigs of either sex (weight 200–300 g). The care and use of the animals in this study were approved by the Administrative Committee on Animal Research in the Tsinghua University Shenzhen Graduate School.

2.1 *Experimental*

Figure 1 shows a schematic of the optical experiment. The output power of the laser (LSR980H-4W, Ningbo Yuan Ming Laser Technology Co., Ltd., Ningbo, China) was modulated by a current source controller (LSR-PS-FA, Ningbo Yuan Ming Laser Technology Co., Ltd., Ningbo, China), which is compatible with transistor–transistor logic (TTL) modulation. The pulse width was modulated by microcontroller unit (MCU) (MC9S12XS128, Freescale Semiconductor, Inc.). The laser output was coupled into a 105-μm diameter optical fiber through a lens fiber coupler (APFC-3AT, Zolix, Beijing, China). The output power, which was measured at the distal end of the fiber, ranged from 0 to 2.2 W and the pulse durations could be as short as 30 μs. An electrophysiograph (RM6240C, Chengdu Instrument Factory, Chengdu, China) was used to collect the signals, which were transmitted to the computer.

2.2 *Anesthesia and Surgery*

All guinea pigs were anesthetized by an initial intraperitoneal injection of 20% ethyl carbamate (6 mL/kg body weight) before the experiment; if the animal showed signs of increasing arousal, maintenance doses of about 3 mL/kg body weight

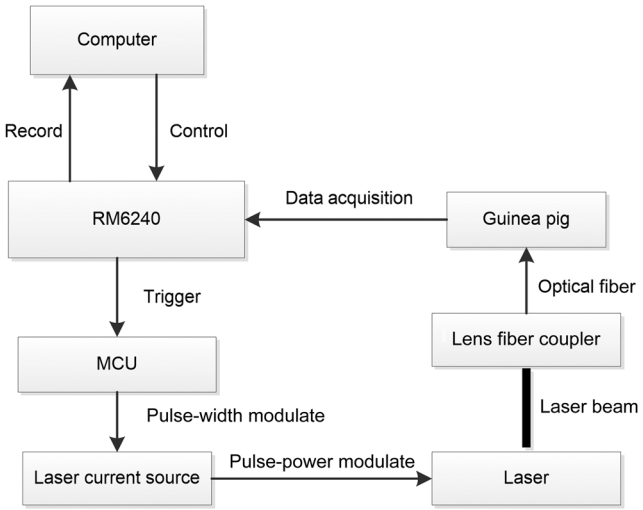

Fig. 1 A schematic of the optical experiment. The output power of the laser was modulated by a current source controller, which is compatible with transistor–transistor logic (TTL) modulation. The pulse width was modulated by microcontroller unit (MCU). The laser output was coupled into a 105-μm diameter optical fiber through a lens fiber coupler. The output power, which was measured at the distal end of the fiber, ranged from 0 to 2.2 W and the pulse durations could be as short as 30 μs. An electrophysiograph was used to collect the signals, which were transmitted to the computer.

were administered. After the animal corneal reflection disappeared, it was fixed onto an autopsy table with a heating pad (BORO, BR Pet Products Co., Ltd., agent in Dongguan, China) to maintain the temperature of the guinea pig at about 38 °C.

To access the cochlea, we cut off the pinna and removed the reticular tissue around the ear hole on the skull to entirely expose the ear hole and mastoid bone behind the ear. Access to the cochlea was obtained by drilling a hole of approximately 2 mm in diameter on the mastoid bone, and then enlarging the hole to visualize the round window.

Once acoustically induced CAPs (aCAPs) were acquired and the efficacy of laser stimulation was confirmed in a normal hearing animal, extensive surgery was done to deafen the animal in order to confirm that the subsequent CAPs were induced by optical stimulation instead of acoustic stimulation. We enlarged the hole with a tweezer and then removed the tympanic membrane along with the ossicular chain to eliminate the interference from the noise to the response of the cochlear. Figure 2 shows the auditory neural response from the acoustic stimulus before and after the deafening surgery. The amplitude of the aCAP between N1–P1 is more than 400 μV before deafening, while after surgery no obvious aCAPs were evoked by acoustic stimuli.

For optical stimulation, the output of laser was coupled to an optical fiber, 105 μm in diameter, which was fixed on a micromanipulator (MP-225, Sutter Instrument Company, agent in Beijing, China). The end of the optical fiber was placed in proximity to the round window membrane and was visually oriented toward the spiral ganglion cells in Rosenthal's canal in the basal turn. The base of the cochlear is sensitive to high frequency, while the apex is sensitive to low frequency. Therefore, the area we stimulated is sensitive to high frequency. A silver electrode (XF100, Chengdu Instrument Factory, Chengdu, China) was placed at the promontorium tympani, which was near

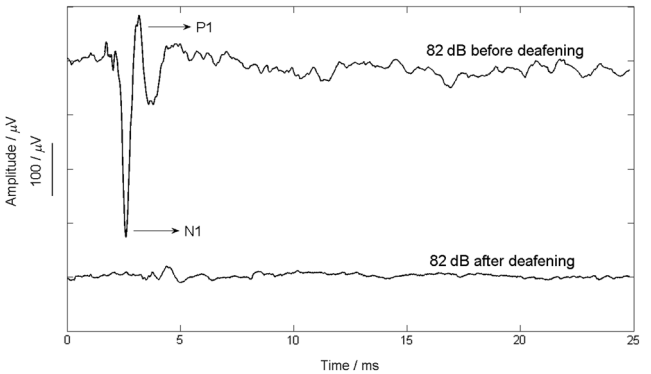

Fig. 2 The auditory neural response from the acoustic stimulus before and after the deafening surgery. The amplitude of the aCAP between N1–P1 is more than 400 μV before deafening, while after surgery no obvious acoustically induced compound action potentials (aCAPs) were evoked by acoustic stimuli.

the oval window, to serve as a recording electrode. The relative locations among the optical fiber, silver electrode, and cochlea are shown in Fig. 3.

2.3 *Stimulation and Signal Acquisition*

After surgery, the guinea pig was transferred to a soundproof room. Both aCAPs and oCAPs were measured by an electrophysiograph (RM6240C, Chengdu Instrument Factory, Chengdu, China). Both aCAPs and oCAPs were filtered between 50 Hz and 1 kHz with a 100 kHz sampling rate. Three electrodes were used for data acquisition. A silver electrode (XF100, Chengdu Instrument Factory, Chengdu, China) was placed at the promontorium tympani, which was near the oval window, to serve as a recording electrode. A reference electrode was clipped into the auricular skin and a ground electrode was inserted into the dorsal skin of the guinea pig. To reduce the influence of random error on the final measurements, all CAP signals were reported as the average of 30 signals that were obtained based on synchronization between the detector and the stimulus. All data were analyzed offline in MATLAB® R2013a.

Acoustically evoked CAPs were achieved by stimulation with a tone burst produced by a speaker [SPA2380/93, Philips (China) Investment Co., Ltd., Shanghai, China] at 82 dB SPL and operated at 0.5 Hz.

oCAPs were achieved by stimulation with a 980-nm diode laser whose pulse duration was adjustable from 30 μs to 1 ms. The output power of the optical fiber (0 to 2.2 W) was controlled by the current source of the laser and measured with a power meter. According to ultrastructure studies of the round window membrane of humans, monkeys, felines and rodents, rodents have the thinnest round window membrane.[28] The mean thickness of the round window membrane in young mice is 11 μm.[29] As guinea pigs and mice both belong to the rodent family, they have similarly thin round window membranes. Furthermore, the round window membrane is translucent. Therefore, we ignore the affection of the round window membrane to the spot size. The numerical aperture of the fiber is 0.2. The distance between the end of the fiber and the spiral ganglion cells in the Rosenthal's canal is approximately 1.03 mm and the spot size is about 0.21 mm^2 inside the cochlear. The calculated radiant exposures ranged from 0 to 53.2 mJ/cm^2 at a pulse duration of 50 μs. All the oCAPs were recorded after deafness in order to eliminate interference from ambient sound.

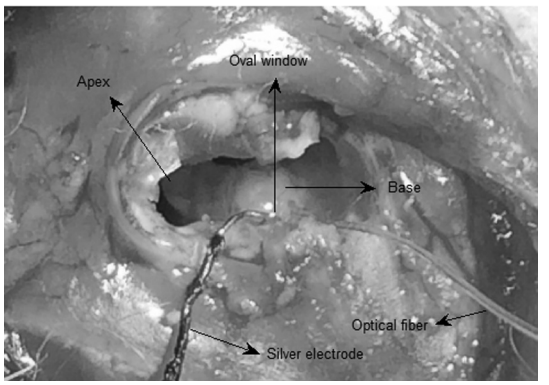

Fig. 3 The relative locations among the optical fiber, silver electrode, and cochlea.

To synchronize the optical stimulus and the data recording, we used a trigger signal produced by an electrophysiograph (RM6240C, Chengdu Instrument Factory, Chengdu, China), to drive the microcomputer. When the MCU detected the rising edge of the interrupt signal, it delivered the predefined TTL signal at a certain pulse width to the current source of the laser, and initiated data acquisition in the computer. The synchronous effect is plotted in Fig. 4. The data in Fig. 4 were derived from a Ge biased photodetector (DET50B/M, Thorlabs, Inc.) and recorded by the RM6240C electrophysiograph.

3 Results

3.1 *Comparison between Acoustically Induced Compound Action Potentials and Optically Evoked Compound Action Potentials*

Figure 5 shows the typical waveforms of aCAPs [Figs. 5(a) and 5(b)] evoked from a normal hearing guinea pig before deafening and oCAPs [Fig. 5(c)] evoked from a normal hearing guinea

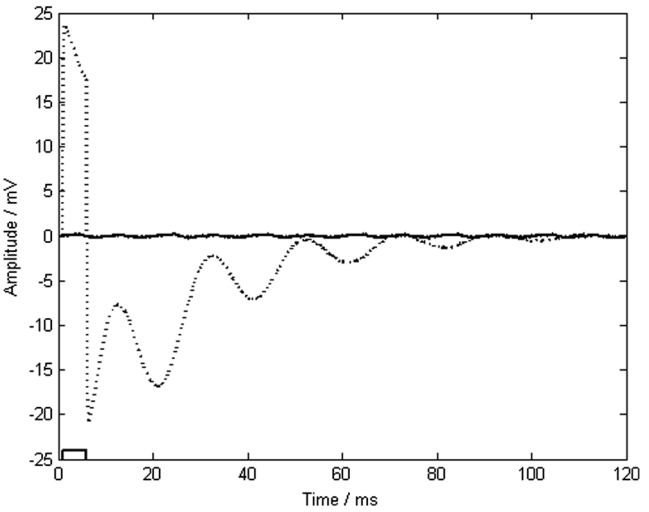

Fig. 4 The solid line shows the data gained from the photodetector when the laser was off. The dotted line was acquired when the laser was on. The rectangle at the time of 1 ms indicates the start of stimulation. The pulse width of the stimulation was 5 ms. The dotted line shows that the response and stimulation were well synchronized. The noise seen in the dotted line is electrical noise from the laser current source at the frequency of 50 Hz.

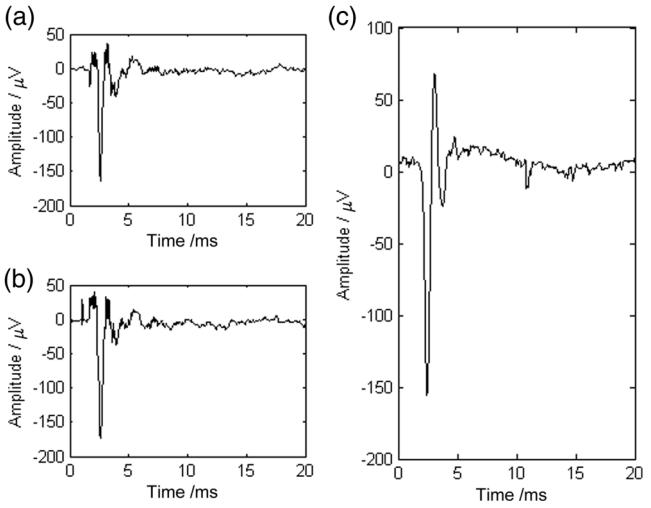

Fig. 5 The acoustically and optically evoked compound action potentials. (a, b) CAPs induced by positive voltage and negative voltage are respectively shown. (c) Optically induced CAPs are shown with 50 μs pulse width and 53.2 mJ/cm^2. The stimulation time of all the CAPs was delayed by 1 ms.

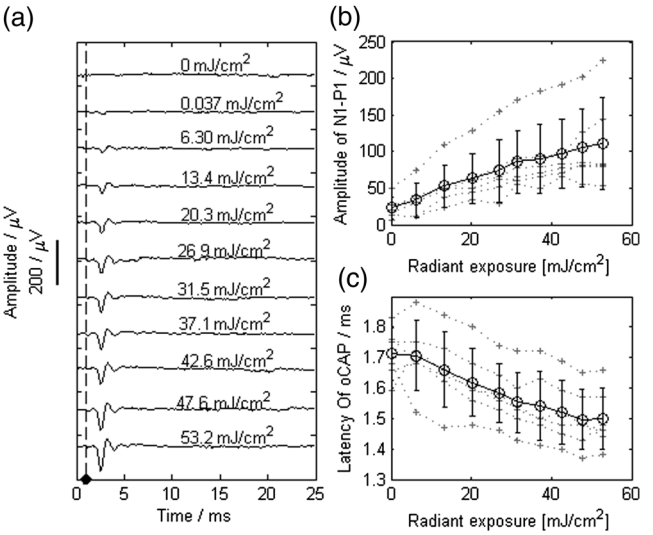

Fig. 6 (a) Representative optically stimulated CAPs obtained upon increasing the intensity of the stimulus at a pulse width of 50 μs. The dashed line at the time of 1 ms indicates the starting point of stimulation. (b, c) The average amplitude of N1–P1 and latency of N1 for all animals are plotted as black circles with standard error bars. Each individual set of data is plotted with as gray circles, $n = 6$.

pig after deafening. Acoustically evoked compound action potentials were achieved from two acoustic tone bursts at 80 dB SPL with a 180 deg phase difference and optically evoked ones were recorded with radiant exposures 53.2 mJ/cm^2. We started the stimulus at the time of 1 ms. Both aCAPs and oCAPs have a latency ranging from 1.0 to 2.0 ms which is calculated from the starting point of stimulation to the minimum of N1. The N1 of CAPs reached its minimum at about 1.5 ms. Furthermore, no cochlear microphonic can be seen in the optically induced CAPs.

3.2 *Optically Evoked Compound Action Potentials with Different Radiant Exposure*

To explore the relationship between radiant exposures and amplitudes of oCAPs at 980 nm, the power at the end of the optical fiber was gradually increased from 1.52 to 2190 mW, with the corresponding radiation exposure ranging from 0.037 to 53.2 mJ/cm^2 at a pulse duration of 50 μs. According to our results in Fig. 6(a), which shows oCAPs recorded at different radiant energy, there is an intensity threshold above which optical stimulus can generate oCAPs. When the radiant exposure was below the threshold, no oCAPs were recorded. As the radiant energy was increased, the recorded amplitude of oCAPs gradually increased and the differentiation of N1 as well as P1 became more obvious. However, most of the amplitude of oCAPs did not obviously increase when the radiant exposure was above 30 mJ/cm^2. Thus, optical stimulus could trigger the response of the auditory nerve on the condition that the radiant exposure exceeds a certain threshold and the intensity of the stimulus is within a specific range, which is shown in Fig. 6(b). It is evident from Fig. 6(c) that increasing the radiant exposure shortened the latency of N1, which ranged from 1.9 to 1.3 ms.

3.3 *Optically Evoked Compound Action Potentials with Same Radiant Exposure under Different Pulse Duration*

As shown in Fig. 6(a), the amplitude of oCAPs increased as the radiant energy increased at a pulse duration 50 μs. We also explored the influence of pulse duration on oCAP at constant radiant exposure (37.1 mJ/cm^2). The data in Fig. 7 show that under the same radiant energy, increasing the pulse duration reduces the amplitude of oCAPs.

3.4 *Optically Evoked Compound Action Potentials with Different Stimulus Rate*

To identify the most suitable stimulus parameters, we also explored the influence of stimulation rate upon optically induced CAPs. Figure 8(a) shows the oCAPs obtained by varying the stimulation rates from 182 to 1000 Hz with a constant pulse width of 50 μs. All the data are reported as the average of 30 readings. N2 in the oCAPs was evident at stimulation rates of less than 400 Hz, however, at stimulation rates above 667 Hz, only N1 and P1 can be seen. This is mainly due to the latency of N1, approximately 1.5 ms [Fig. 6(c)], which restricts the maximum discharge rate. In addition, we calculated how the amplitudes of N1 and P1 respond to optical stimuli at different repetition rates. With increasing stimulus rate, the amplitude decreased, which can be seen in Fig. 8(b).

4 Discussion and Conclusion

Most of the previously published studies on optical neural stimulation have focused on visible light and long-wavelength near-infrared light (>1800 nm). Our experiments proved that a shorter-wavelength near-infrared pulsed laser (980 nm) can elicit CAP from a deafened guinea pig cochlea [Fig. 5(c)], suggesting the use of a short-wavelength near-infrared laser as an alternative stimulus for cochlea implants. Compared with the acoustic stimulation, optically induced CAPs had no microphonic potential during the incubation period, and both aCAPS and oCAPs approximately exhibited the same latency. Furthermore, the latency of oCAPs decreased as the radiant exposure was increased at a fixed pulse duration of 50 μs [Fig. 6(c)]; this behavior is similar to that of aCAPs whose

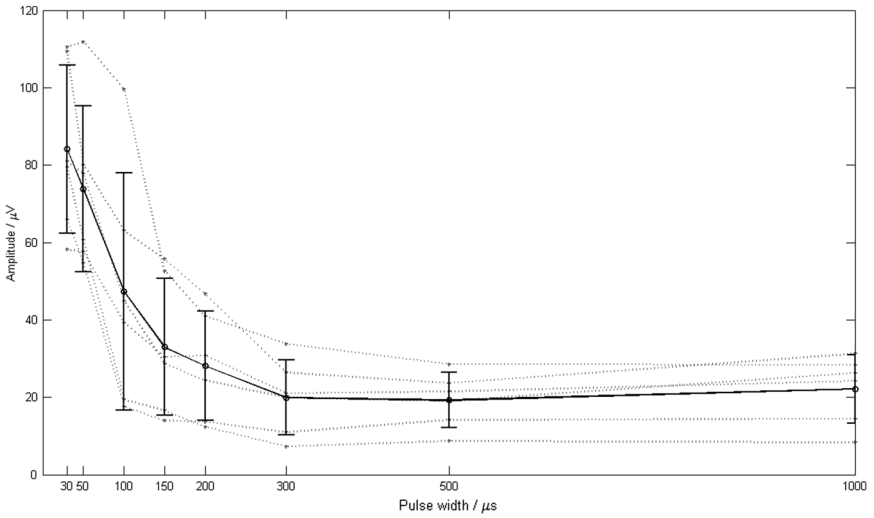

Fig. 7 Amplitude of oCAPs at constant radiant exposure and varying pulse duration from 30 to 1000 μs, $n = 6$. The data are averaged with standard error bars.

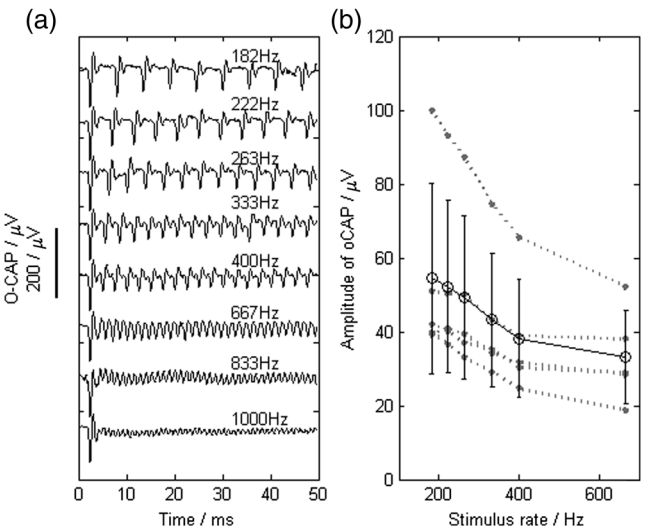

Fig. 8 (a) Typical oCAPs obtained at different stimulus rates. The data are reported as the average of 30 signals. (b) Amplitude of oCAP as a function of stimulus rate. The average amplitude of N1 and P1 at different stimulus rate for all animals is plotted as black circles with standard error bars. Each individual set of data is plotted as gray circles, $n = 5$.

latency decreases as the level of sound pressure is increased. The average latency of oCAP is 1.6 ms [Fig. 6(c)].

Comparing Fig. 6(a) with Fig. 7, it is evident that with increasing intensity of radiant exposure, the oCAPs' amplitude correspondingly obviously increases when the radiant exposure is under 30 mJ/cm^2 and increases slowly when the radiant exposure is above 30 mJ/cm^2. The CAP amplitudes recorded in this study were larger than 808 μm at the same radiation exposure.[27] This result can be attributed to differences in pulse duration at fixed radiant exposure.

Under the same radiant exposure, the amplitude of oCAPs decreased as the pulse duration increased, which indicates that laser stimulation of oCAPs is not governed by the total energy of laser exposure, but rather the time over which the energy is deposited; that is, the laser power. We can see the same trend in Fig. 5 for 1.94 μm wavelength.[19]

As for the 808 nm wavelength[27] in Fig. 4 and for the 1.94 μm wavelength[19] in Fig. 5, they examined the CAP amplitude at the different pulse durations of 300 and 100 μs, respectively. In our experiments, we examined the CAP amplitude at the pulse duration of 50 μs for the wavelength of 980 nm. We can see that the laser peak power rather than the total radiant exposure plays a more important role with the same wavelength in Figs. 6(a) and 7. Therefore, before comparing the power requirements with different wavelengths, we must make sure that they compare under the same laser peak power.

For the wavelength of 980 nm, the amplitude of oCAP at a pulse duration of 50 μs is approximately 100 μV at a radiant exposure of 50 mJ/cm^2 in Fig. 6(b) in our experiments. While for the wavelength of 808 nm,[27] the amplitude of oCAP at the pulse duration of 300 μs is approximately 80 μV at a radiant exposure of 300 mJ/cm^2 in Fig. 4. Additionally, for the wavelength of 1.94 μm,[19] the amplitude of oCAP at the pulse duration of 100 μs is greater than 300 μV at a radiant exposure of 100 mJ/cm^2 in Fig. 5. In conclusion, under the same laser peak power, the amplitude of oCAP for the wavelength of 1.94 μm is the largest and the amplitude of oCAP for the wavelength of 808 nm is the smallest. The amplitude of oCAP for the wavelength of 980 m is the exactly between the amplitude of oCAP for the wavelength of 808 nm and 1.94 μm, which is similar to the absorption coefficient of water for different wavelength. We can see that a high wavelength with the higher absorption coefficient of water leads to a higher amplitude of the oCAP, in other words, it needs a lower laser peak power. To some extent, it verifies that the photothermal effect is the underlying mechanism by which the laser stimulus triggers CAPs.

The first oCAPs' amplitude of every waveform in Fig. 8(a) is the largest. This is because this amplitude is the first response and is due to the synchronization of stimuli. Higher repetition rates lead to smaller oCAPs' amplitudes under the same intensity of stimulation; this information could guide the future design of optical cochlear implants.

It is widely believed that the photothermal effect is the underlying mechanism by which a laser stimulus triggers CAPs. We can see from Fig. 6(b) that the latency of N1 shortened with the increasing radiant exposure. Therefore, to some extent it verifies the photothermal effect. However, to explore this mechanism

will require further experiments that include monitoring the temperature change of the cochlea or the vibrations of the round window membrane in real time. Additional studies in our group will also explore the effects of multiple stimulation channels, a typical feature in many cochlear implants.

Although our experiments provided some evidence that a laser with a wavelength of 980 nm could induce CAPs, further experiments are needed in order to optimize the system, such as for the deafening protocols. There were several effective ototoxic deafening protocols to eliminate hair cell fuction.[30–32]

In conclusion, stimulation with a laser of 980 nm wavelength can successfully induce CAPs outside the cochlea. Furthermore, the results of our research into the effects of pulse duration, laser power, and radiant exposure provide information about optical parameters relevant to improving the design of optical cochlear implants toward their eventual application in the human cochlea.

Acknowledgments

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