Published in final edited form as:

Proc SPIE. 2013 March 8; 8565: 85651Y–. doi:10.1117/12.2010337.

Infrared neural stimulation in the cochlea

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Abstract

The application of photonics to manipulate and stimulate neurons and to study neural networks has gained momentum over the last decade. Two general methods have been used: the genetic expression of light or temperature sensitive ion channels in the plasma membrane of neurons (Optogenetics and Thermogenetics) and the direct stimulation of neurons using infrared radiation (Infrared Neural Stimulation, INS). Both approaches have their strengths and challenges, which are well understood with a profound understanding of the light tissue interaction(s). This paper compares the opportunities of the methods for the use in cochlear prostheses. Ample data are already available on the stimulation of the cochlea with INS. The data show that the stimulation is selective, feasible at rates that would be sufficient to encode acoustic information and may be beneficial over conventional pulsed electrical stimulation. A third approach, using lasers in stress confinement to generate pressure waves and to stimulate the functional cochlea mechanically will also be discussed.

Keywords

infrared neural stimulation; optogenetics; thermogenetics; cochlear implants; optical stimulation

1. INTRODUCTION

Among neural prostheses, cochlear implants (CI) are considered the most successful devices. To date, they restore some hearing in ~219,000 severe-to-profound deaf individuals by stimulating segments along the length of the tonotopically organized cochlear spiral

ganglion with electrical current (<http://www.nidcd.nih.gov/health/hearing/pages/coch.aspx>). The average cochlear implant user can understand running speech under quiet listening conditions. The scores in standard speech recognition tests for many of the patients are more than 50% and can reach close to 100%. However, the performance suffers in noisy listening environments and for music perception [1–5]. Efforts are on the way to improve cochlear implants by the development of better coding strategies and by improving the electrode-tissue interface. The design of speech processors for cochlear implants assume that each electrode contact is distinct, both spatially and temporally, or equivalently that electrode interaction (i.e. overlap in fields of stimulation) does not occur. However, electric current spreads in tissue and electrode interaction does occur, sometimes with deleterious effects [6–13]. Contemporary cochlear implants have up to 22 electrodes, but only 4 to 7 electrode contacts can be considered independent [14–16]. In contrast, a normal hearing subject is estimated to process 30–50 independent channels [16]. As a consequence, conventional cochlear implants poorly restore the normal hearing system's high fidelity. It has been suggested that speech recognition in noisy environments and music appreciation would benefit from an increased number of independent perceptual channels available for the listener [17–19]. Therefore, efforts in the development of future cochlear implant electrodes include increasing the number of discretely stimulated populations of spiral ganglion cells.

1.1 Novel design considerations for neural prostheses

Several strategies have been employed to increase the spatial selectivity of electrical stimulation (ES) over a conventional monopolar stimulation paradigm. Multipolar electrode configurations have been employed to increase the spatial selectivity of stimulation [20–23] or to introduce virtual channels [24–27].

However, the use of either virtual channels or tripolar stimulation only showed marginal improvement in performance [20–27]. The limited improvement might be explained by the fact that multipolar stimulation and virtual channels did not result in an increase in the number of independent channels that can be used at the same time. Recently, penetrating electrodes have been explored for more spatially focused stimulation by inserting the stimulating source into the nerve tissue [28–30]. General challenges for penetrating electrodes include the potential damage of the nerve by the insertion of the electrode into the tissue [31, 32] and from inflammation or edema [33, 34] following the placement of the electrode.

2. PHOTONICS FOR NEURAL STIMULATION

A key emerging technology in the field of neural excitation is the application of light to stimulate small populations of neurons. Photonic methods, due to the inherent ability to focus light to micron-level spots, present a fundamental paradigm shift in the field of neural stimulation [35, 36]. Light of the appropriate parameter set can reliably evoke or inhibit neural action potentials in a non-contact manner [35, 37]. The following novel approaches have evolved over the last decade, (1) stimulation of neurons after light sensitive ion channels have been expressed in the cell membrane (optogenetics), (2) stimulating heat sensitive channels which have been expressed in the plasma membrane of neurons (thermogenetics), (3) the direct interaction of the radiation with the cell by changing the

cell's membrane capacitance through spatially and temporal confined heating with a laser pulse (INS), (4) the intracellular modulation of calcium with infrared laser pulses [38, 39]. Furthermore, photonic neural stimulation also eliminates potentially harmful by-products of the electro-chemical reactions involved in electrical stimulation. Unlike in electrical stimulation, optical stimulation contains no stimulation artifact [40]. Despite the excitement for the novel methods, the techniques have challenges too. In the following the methods are discussed in more detail.

2.1 Optogenetics

The field of optogenetics has been growing rapidly and during the last year several excellent review papers appeared (for example see [37, 41–44]). Opsins have been studied since the 1970s for their ability for light driven ion transport [42, 45, 46]. Only recently, almost four decades later, the first paper appeared that showed the expression of such ion channels in selected cells, including neurons, to be used as a tool to control neural activity [47]. Following the first publication in 2005, it took only several months until the expression of ion channels in neurons became a popular tool for controlling and studying complex neural networks. The first ion channels that were used for the investigations were a light-driven inward cation channel, channelrhodopsin-2 (ChR2) and a light driven inward chloride pump, halorhodopsin (Halo). While ChR2 is an excitatory channel, Halo inhibits neural activity [41, 47]. The initial results demonstrated that ChR2 and Halo, when expressed at a sufficient rate and stimulated with light, could depolarize and hyperpolarize neurons. The findings gave also hope for the improvement of neural prostheses. The implementation of optogenetics in restoring vision is one of the advanced efforts in using the technology for prostheses [48]. In the retina, the typical irradiance at the target neuron, which is required for stimulation, is about 100 mW/cm^2 [48]. Typical pulse lengths are between 1–10 ms at a radiant wavelength of 470 nm (blue light). For comparison, the intensity of the blue light for stimulation threshold corresponds to about 10^5 – 10^6 cd/m^2 , which is two to three orders of magnitude larger than the brightness of a LCD plasma screen ($2.5 \cdot 10^2$ – 10^3 cd/m^2 at $\sim 532 \text{ nm}$). The required photon flux for stimulation is significant and will also heat the target tissue. One paper has estimated that the local and transient temperature elevation exceeds 10°C [48]. In contrast to the visual system, the irradiance to stimulate the hippocampus *in vivo* was 0.1 – 5 mW/mm^2 . For the latter conditions, the temperature increase has been estimated to be about 0.3 K [37]. A different challenge for optogenetics will be the dynamics of ChR2 and its mutants [43], which is determined by the channel's nonlinear behavior and protein intrinsic adaptation [49, 50]. Published results reveal a rate limit of the responses to typically less than 50 Hz [43, 47, 49–56]. Some recent developments suggest that the ChETA mutation allows rates up to 200 Hz [56]. As ChR2 is a nonspecific light-driven inward cation channel it also allows protons to enter the cell during stimulation. It will be important to document that continuous stimulation at the maximum rate of the channel will not challenge the cell's homeostasis, in particular the cell's pH.

2.2 Thermogenetics

Recently a new term has been christened, thermogenetics. It describes the expression of thermosensitive ion channels, including the transient receptor potential cation channel of the vanilloid subfamily (TRPV) in the plasma membrane of neurons. Subsequent heating of the

neurons with a fast heat source, such as an infrared laser, can be used to depolarize the neuron. In the past, it has been argued that naturally occurring TRPV channels can be activated by thermal confined stimuli. Recently published data confirm that neurons can be stimulated by activating of temperature sensitive ion channels such as the TRPV channel [57, 58].

2.3 Infrared Neural Stimulation (INS)

At present, INS has been tested in various peripheral nerves, in cranial nerves, the brain, and in the heart [e.g. 59, 60]. In particular, the sciatic nerve and the auditory system have been well studied. Although differences between the two neural systems exist, (e.g. stimulation threshold roughly an order of magnitude smaller in the auditory system) in all of the experiments, the lack of a large stimulation artifact and the spatial precision have been noted as the primary characteristics of INS to drive innovation in neural stimulation [59]. Studies using the wavelength-tunable free electron laser demonstrated that optimal wavelengths (those with the largest safety margin between stimulation and damage threshold) for extraneural stimulation of mammalian peripheral nerves depend on the water absorption spectrum, likely because water is the dominant tissue absorber in the IR. Typical wavelengths for INS are between 1844 and 2120 nm [35, 61–63]. Alternative wavelengths (1400 – 1600 nm), with similar water penetration depths, are also suitable for INS [64]. For the latter wavelengths, the pulse durations at which depolarization was shown, were significantly longer (~100 ms) and the fluences were higher than those demonstrated in previous experiments. Using a 1540 nm implantable laser from LMA we have verified in the guinea pig that stimulation of the auditory system at this wavelength is possible (unpublished results).

While optogenetic capitalized from its ability to excite or inhibiting neurons in their firing by using different colored radiation (typically blue and yellow), INS took advantage from its selective stimulation. INS likely provides more independent channels for simultaneous stimulation of a neural system, here the cochlea. Recordings from the guinea pig inferior colliculus have shown that INS could be as selective as stimulation with pure tones, and about twice as selective as bipolar electrical stimulation [65], and is at least four times more selective than monopolar stimulation. The temporal properties of cochlear optical stimulation measured at the inferior colliculus compare well with the rates and temporal properties obtained for pure tone or for electrical stimulation. Safety has been demonstrated in cat animal model. Cochlear function remained stable over six weeks of stimulation, six hours each day.

Initial efforts to determine the mechanism for INS indicated that a thermal confined heating of the target structure is required. The exact mechanism by which the heat results in an action is still under investigation. While earlier reports discussed general mechanisms including the activation of temperature sensitive ion channels, it has been demonstrated in a recent paper that infrared light can excite cells through a electrostatic mechanism. Infrared pulses are absorbed by water, producing a rapid local increase in temperature. This heating reversibly alters the electrical capacitance of the plasma membrane, depolarizing the target cell. This mechanism is fully reversible and requires only the most basic properties of cell

membranes. Assuming that water is the sole absorber, the radiation wavelengths correspond to penetration depths of 100 to 1500 μm . In other words, the radiation energy at the tip of the optical fiber or at the radiation source decreases with each penetration length by about 10 dB. Therefore, usable wavelengths for INS have to consider the distance and the materials of the absorbers between the radiation source and the target neurons. Minimizing the fluid distance between the stimulating source and the neural tissue will increase the success of INS. The above statements only take absorption of radiation by the tissue into account. The presence of highly scattering tissue in the optical path, such as bone, may increase spot size and decrease selectivity of optical stimulation.

In the vestibular system and for cardiomyocytes it has been shown that the effects of INS on the intracellular calcium concentration are an important factor for INS. The radiation of the cells increases the intracellular calcium concentration from internal calcium stores.

2.4 Photoacoustic stimulation with IR

Experiments were conducted with laser parameters set for stress confinement. Stress confinement indicates that the laser pulse is shorter than a stress relaxation wave that results from the heating of the target volume would take to travel out of the target volume. This is typically less than 1 μs . A stress relaxation (pressure) wave can stimulate the target structure(s) mechanically. This is of particular interest in the cochlea where hair cells can be stimulated mechanically. Experiments have been performed with a Nd:YAG laser (532 nm, 10 ns) to induce such pressure wave and to stimulate the cochlea mechanically [66, 67].

Pressure waves also occur in thermal confinement. Laser pulses are typically longer than 1 μs and are short enough that the heat dissipation from the target volume is negligible during the irradiation. A series of published experiments has quantified the pressure generation during laser stimulation with an 1850 nm laser and with a laser that has a large range in wavelength (532 nm to 2100 nm) [68, 69]. The laser pulses were typically 3 and 8 ns long and the radiant energy was between 0 and 8 $\mu\text{J}/\text{pulse}$. Resulting pressure waves were able to stimulate the cochlea of a normal hearing animal. It has been discussed elsewhere in detail that this pressure waves unlikely contribute to INS [65, 70]. Rather neural stimulation results from a direct interaction between the radiation and the neuron. [71].

2.5 Direct comparison between the methods

Features			
	Optogenetics /thermogenetics	INS	Photoacoustics
		Thermal confinement	Stress confinement
Mechanism	Expression of light or temperature sensitive ion channels in the plasma membrane. The ion channel/transporter expressed determines the sensitivity to the radiation wavelength and whether inhibition or excitation occurs.	Confined heating of the plasma membrane. Heating is slow enough ($>1 \mu\text{s}$) that stress waves can travel from the heated volume but the heat delivered still remains confined in the target volume. Radiant energy and pulse length determine whether	Radiant energy is delivered faster than a stress relaxation wave can travel out of the heated volume ($\ll 1 \mu\text{s}$), which can result in the generation of considerable stress waves and pressure build-up. Diameter of

		stimulation results in excitation or inhibition.	the optical fibers were 50 and 200 μm .
Wavelength	441, 450, 470, 485, 500, 535, 540, 545, 560, 566, 590 nm.	Typically, but not limited to 1400–1600 nm and 1840–2100 nm	Typically, but not limited to 532 nm and 420–2150 nm
Laser parameter	Pulse length 1–10 ms, irradiance 10–100 mW/cm ²	Pulse length 5 μs to several ms, pulse repetition rate up to 1 kHz tested, threshold radiant exposure $\sim 15 \mu\text{J}/\text{cm}^2$ to 1500 $\mu\text{J}/\text{cm}^2$	Pulse length is typically 3–10 ns, pulse repetition rate 10 Hz, 0–26 $\mu\text{J}/\text{pulse}$
Temporal properties	Typically less than 50 Hz, a novel mutant, ChETA, responds up to 200 Hz.	Sustained CAP responses shown up to 1 kHz; single fiber responses ~ 100 –150 Hz. Onset response times ~ 2.5 ms	Not documented
Challenges			
“chromophore”	Viral vectors are used for targeted and selective expression of ion channels in selected types of neurons or tissue.	Since water is the main absorber for IR, the stimulation source must be close to the target structure; neuron specific stimulation is not possible	
pH changes	Sustained stimulation changes cell ion homeostasis (e.g. pH) with a risk of subsequent cell damage	Not documented	
Heating of tissue	Not documented; estimates of temperature increase during stimulation differ depending on the application.	Limits rate and maximum radiant exposure of stimulation	
Pressure wave formation	Not documented	Stress relaxation waves are generated and can result in photoacoustic stimulation	

3. SUMMARY

Photonics for neural stimulation has become an important tool for neuroscience over the last decade. Maturing of the technique has also great potential for neural interfaces. The advantages are independent of the approach that could be inducing light sensitive or temperature sensitive ion channels into the target neuron by genetic methods or the direct stimulation of the target structures with infrared radiation. All approaches have their strengths and have their limitations. Knowledge of the features of the radiation sources, the target tissues, and the radiation-tissue interaction is important to understand advantages and limitations of the technique and should be given more consideration.

Acknowledgments

This project was funded with federal funds from the NIDCD, R01 DC011855-01A1, DC011481-01A2 and by Lockheed Martin Aculight.

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