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Effects of Prolonged Stimulation at the Electrode-Retina Interface

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Abstract—**Prolonged electrical stimulation can lead to temporary or permanent changes in neural response. Stimulation of neurons at levels sufficient to cause overlapping zones of excitation can induce multiple effects, leading to permanent damage to neurons or temporary depression not detectable through histopathological analysis. The present study focuses on determining the effects of prolonged, continuous electrical stimulation in the retina. One hour stimulation was performed in the rat retina and electrically evoked responses in the superior colliculus were recorded before and after the continuous stimulation. Comparison of the pre and post stimulation responses indicates a depression in the excitability of the neurons.**

I. Introduction

Electrical stimulation of the central nervous system has been found to be an effective albeit an unnatural way of causing neuronal excitation. Most neural prostheses aim to restore lost functionality by stimulating the target neurons. The success of any such prosthesis will depend not only upon the degree of excitability produced but also upon parameters like long-term stability, degree of invasiveness, easy patient handling etc. Devices employing electrical stimulation use stimulation strategies based upon the characteristics of the targeted cells. However, all such prostheses in addition to providing adequate stimulation for neuronal excitation also have to do so without causing damage to the biological tissue and surrounding environment.

Efforts have been made to characterize the important parameters that need to be considered during short term or long term stimulation both for the electrode material and the biological tissue. An optimal combination of the different parameters ensures no irreversible tissue damage or electrode material dissolution. However, recently a more subtle form of damage has been observed which cannot be characterized by histopathological changes in the tissue. Despite using stimulation strategies employing safe limits, a depression in neuronal excitability has been observed. This depression although found to be reversible in nature, persisted for as long as 18 days [1].

For any prosthesis to be successful over any period of time, it becomes imperative to understand and investigate causes for such depression. The current study focuses on understanding and defining the limits of safe stimulation at the electrode-retina interface. It specifically aims at determining the presence of reversible depression in neuronal excitability and understanding the cause of such depression. The entire study was performed *in vivo* in the rat retina, both in normal and degenerate models. Electrical stimulation of the retina was performed while resulting electrically evoked potentials at the superior colliculus (SC) were recorded. The neural responses were recorded before and after performing 1 hour of continuous stimulation of retina. On comparing the responses recorded prior to the 1 hour stimulation to those recorded after, a marked depression in neural excitability was observed.

It has been known that electrical stimulation causes neuronal excitation by inducing a voltage gradient, or a function thereof, across or along the neural elements [2]. However, this stimulation can also induce neural injury when performed at high values of current both for long and short durations. Neural injury may be inflicted either via the electrochemical processes associated with the current injection across the metal electrode-physiologic fluid interface or by those associated with the flow of current through the tissue. Safe limits of stimulation have been divided into two main categories: neural damage limits and electrochemical limits. *Neural damage limits* are mediated by the ability of biological tissue to withstand electric current without any degradation. These are defined in terms of charge density and charge/phase values. While charge/phase is independent of the electrode size, charge density depends upon the active surface area of the electrode. For small electrodes, a charge per phase of 0.1μC/phase and charge density of 1mC/cm^2 has been found to be the limits of safe stimulation [3]. *Electrochemical limits* are based on the ability of the electrode to store or dissipate electric charge without exceeding the water window, outside of which formation of harmful products start. For platinum the limit is approximately 0.35mC/cm^2. Also, long-term stimulation studies done in normal and blind dogs have shown that an epiretinal prosthesis delivering charge densities of 0.1 and 0.05 mC/cm^2 does not cause any damage evident through histological evaluation of the neural tissue [4]. However, recent work has shown that even while remaining within the safe limits of stimulation, continuous stimulation of biological tissue at some predefined rate does induce selective depression in certain neurons (SIDNE) [1].

II. METHODS

A. Animal Model

The protocol was approved by the University of Southern California Animal Care and Use Committee. Long-Evans pigmented rats (normal, n=5) and S334ter-line-3 (degenerate, n=4) rats were used in these studies.

B. Epiretinal Stimulation

A temporal sclerotomy was made (using a 27 gauge needle) approximately 0.5 mm from the limbus and a concentric bipolar electrode (model CBDRG75, FHC Inc.) was inserted epiretinally into the eye and held in place for the entire duration of the experiment by a translational micropositioner on an articulating arm. The 75 μm inner pole (Pt/Ir) was used as the stimulating electrode and the 300 μm outer cannula (Stainless Steel) as the return. The rounded tip increased the surface. The active surface area was estimated to be 9350 μm^2 based on the dimensions provided by the manufacturer. Biphasic voltage pulses were generated using a stimulus generator (STG 2008, Multichannel Systems). The voltage pulses were fed to an analog voltage-to-current converter (Model 2200, A-M Systems) to give constant current output pulse having the same shape as the input voltage pulse.

C. Superior Colliculus Recording

For recording the neural response, a craniotomy was performed and the SC was exposed. Light and electrically driven evoked potentials were recorded extracellularly from the superficial laminae of the SC using tungsten microelectrodes positioned 100-200 μm below the surface. Electrically evoked potentials (EEPs) were amplified (gain 10^3) and filtered from 300 and 10000 Hz (World Precision Instruments) and then digitized at 20 kHz (Powerlab; AD Instruments). Compound action potentials were recorded starting from 100ms before till 500ms after the onset of the stimulus. A single recording was defined as the average of 20 trials, with approximately 5 seconds in between stimuli.

The location of strongest response to electrical stimulation was found by probing different points in the SC and recording the resulting neural response there. The recording electrode was then held in position at that location and all recording was stopped while the retina was stimulated for 1 hour duration with charge-balanced biphasic current pulses (cathodic first, 150 μA, 1 ms pulse duration, 100 μs interpulse delay) delivered at 100 Hz. After the one-hour period, recording was once again resumed from the exact same location prior to stimulation. Control experiments were also performed where the recording electrode was held in position for 1 hour duration without any stimulation. The pre and post 1 hour responses, for both control and stimulation groups, were then compared to assess the effect of the chronic stimulation.

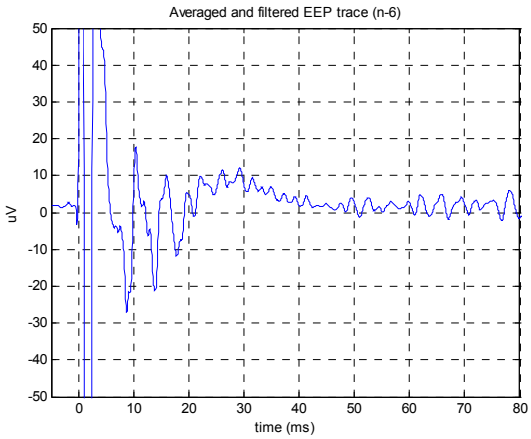


Fig. 1. Example of evoked potential recorded in the SC for the case of normal retina

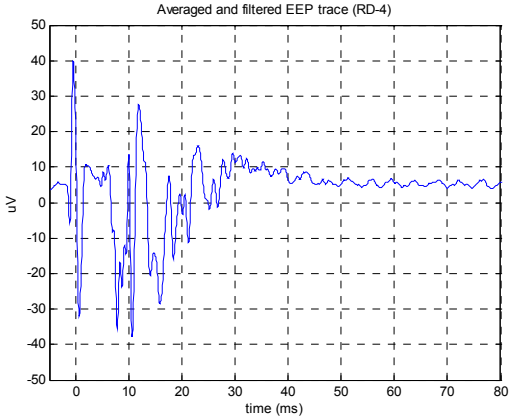


Fig. 2. Example of evoked potential recorded from the SC for the degenerate case

III. RESULT

Preliminary findings have shown a depression in the neural excitability after 1 hour of continuous stimulation. However, no such depression was observed in the control experiments. The thresholds for inducing neural response increased after 1 hour of stimulation both for normal (n) and degenerate (RD) models (fig. 3). The dose response curves recorded for six different stimulus levels were observed to shift downwards after the one hour stimulation period (fig.4).

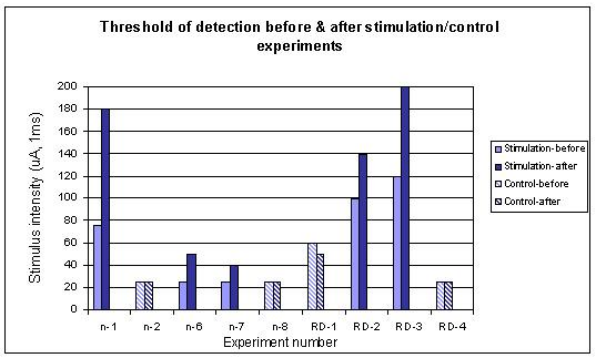
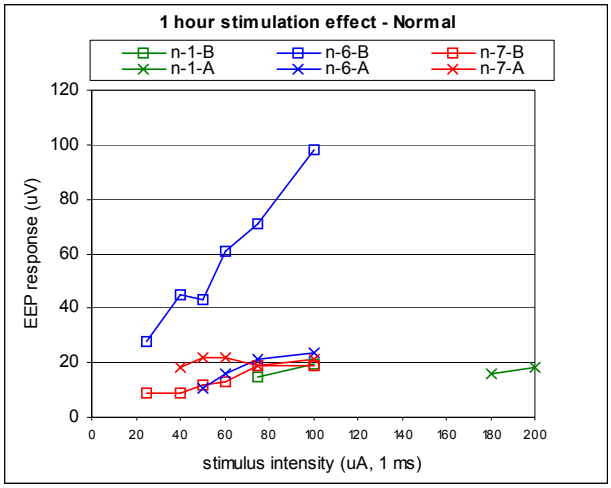


Fig. 3. Graph showing threshold for neural excitation before and after 1 hour period of stimulation/control

(i)



(ii)

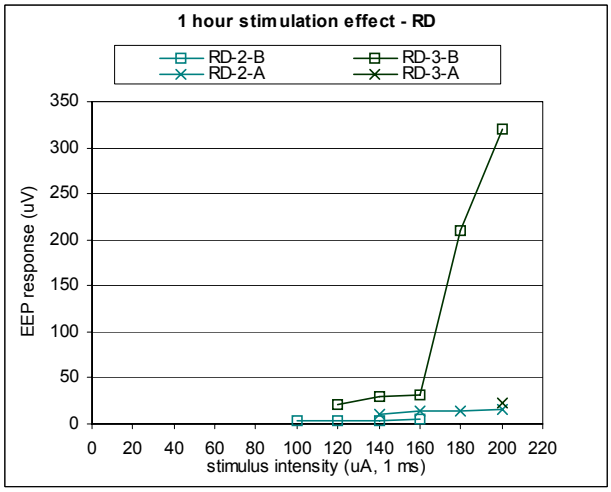


Fig. 4. Stimulus-response curves before and after 1 hour stimulation period for normal (i) and degenerate (ii).
Note: RD3-A is single point only.

IV. DISCUSSION

Electrical stimulation of neurons outside the safety limits has been shown to cause irreversible damage of the tissue. However, even remaining within the safety regime may not guarantee the normal functioning of the neurons. For devices employing continuous stimulation, the frequency and duration of stimulation become important factors to be considered during the design and application stages. The study conducted showed that there is a definite elevation in the threshold of excitation after only 1 hour of stimulation. However, if the stimulus parameters are modeled according to the equation for safe levels of stimulation [5], then for the electrode size used, a safe charge density level of 0.58mC/cm^2 is obtained which is much lower than the charge density level used in the study (1.6mC/cm^2). Also, the charge density applied exceeds the safety limit of platinum. Thus, the increased threshold noted in these experiments is most likely due to tissue damage from high charge density stimulation. However, at this point the possibility of a temporary change in neural excitability can not be excluded. Further work will entail conducting similar studies using lower charge densities (0.35mC/cm^2) to observe the presence or absence of depression. Also, different stimulus frequency levels will be applied to observe the effect of this parameter on evoking neural responses. If depression is observed then by analyzing the histopathology of the stimulated tissue conclusions can be made as to whether the cause of depression is irreversible tissue damage or due to other phenomena like the SIDNE effect.

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