Excitation Characteristics of Paresthesias Produced by Deep Brain Stimulation

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Abstract

Chronic deep brain stimulation (DBS) is effective in treating a number of neurological disorders, but the mechanisms of action are unclear. Current hypotheses are difficult to evaluate because it is not known which neural elements are affected by stimulation. During electrode implantation for DBS therapy, neural recordings are conducted to determine the receptive fields of local neurons. During test stimulation of the thalamus, patients may experience paresthesias either in the local receptive field (concordant paresthesias) or in a different area of the body (discordant paresthesias). We hypothesized that concordant paresthesias are caused by the stimulation of neural cell bodies while discordant paresthesias are due to the stimulation of axons of passage. Strength-duration properties of paresthesias were measured to differentiate stimulation of local cells or axons of passage. No significant differences were found between the chronaxie times of concordant and discordant paresthesias, suggesting that both are evoked by axonal stimulation.

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Introduction/Background

Chronic electrical stimulation of deep brain structures has emerged as a therapy to treat movement disorders resulting from neurological disorders including Parkinson's disease, essential tremor, and multiple sclerosis [1]. However, little is known regarding the mechanism of action of this technique. Knowledge about which neural elements are being stimulated or inhibited will enable further refinement of the therapy and an expansion of the patient population to whom it is available.

As part of the localization of the implantation target, a microelectrode is advanced into the thalamus, and testing is conducted to determine the receptive field and modality of the neurons around the electrode. Additionally, test stimuli are delivered that often evoke paresthesias. If it is felt within the receptive field of the local neuron, the paresthesia is considered to be concordant. Alternatively, if it is felt in a different area of the body, the paresthesia is considered to be discordant. Paresthesias may also be induced during therapeutic stimulation, limiting the efficacy of the therapy [2].

Previous studies have demonstrated that the chronaxie time (T_{ch}) and refractory periods of neural cell bodies are longer than those of myelinated axons [3,4,5]. In this study the excitation characteristics of concordant and discordant paresthesias were measured to determine whether stimulation of cells or axons is responsible for the different paresthesia types

Methods

Participation was offered to all patients diagnosed with multiple sclerosis or essential tremor planning to undergo surgery for deep brain stimulation of the thalamus for the treatment of tremor. All procedures were approved by the Institutional Review Board of the Cleveland Clinic Foundation and informed consent was obtained from all subjects. The initial target was the sensory relay nucleus of the thalamus, ventrocaudal thalamic nucleus (Vc), and the final target for implantation was the ventrointermediate nucleus of the thalamus (Vim). Microelectrode recordings of neuronal activity and microstimulation through the microelectrode were used for physiological target identification. Microelectrodes were platinized-iridium with tip exposures of 10 to 15mm and impedances of approximately 0.6 MOhms at 1000Hz.

Neurons were recorded at various sites along the penetrations in Vc and Vim, and the modality and receptive fields of neurons were determined. Cathodal monophasic stimuli were applied (I<90μA, 330Hz, 0.2ms pulse duration, 800ms train duration), and the patient reported the nature and location of any sensations. Sites were considered to be concordant if the sensory receptive fields matched the distribution of sensations to the lowest threshold of stimulation. The site was considered to be discordant if the receptive field was not contiguous with the distribution of the sensations experienced with stimulation.

Threshold currents (I_{th}) as a function of pulsewidth (PW) were measured for pulsewidths between 20μs and 2ms. Thresholds to evoke a paresthesia were determined by the patient's subjective responses, using a standard up-down paradigm . The step size was 1μA for thresholds in the range of 1-15μA and a step size of 10μA was used for thresholds in the range of 10-90μA. Repeated measures of threshold at a

baseline setting were used to assess consistency across trials.

Threshold data were $\log_{10}$ transformed and fit to the $\log_{10}$ corrected Weiss equation (equation 1), as this has been shown to yield more consistent values for T_{ch}.[6] A χ^2 reduction algorithm was used to solve for the rheobase current (I_{rh}) and T_{ch}.

$$\log_{10} [I_{th}] = \log_{10} [I_{rh} * (1 + T_{ch} / PW)] \quad \text{(equation 1)}$$

The frequency tuning curve of the paresthesias was determined by measuring the threshold at 70, 140, and 330Hz. Refractory periods were determined using a paired-pulse paradigm to measure changes in threshold for evoking paresthesias as a function of the interpulse interval [7]. If the interpulse interval was shorter than the refractory period, then the effective frequency of a train of stimulation was decreased by half, and the threshold increased as determined by the frequency tuning curve.

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Results

Thirteen units were recorded from 9 patients. Seven of these recordings were disqualified due to inconsistencies in patient responses to identical stimuli. Trials were defined as inconsistent when the average percent deviation of the threshold for fixed stimulation parameters was greater than 20%.

The mean chronaxie time for all of the paresthesias was 0.41ms. Two of the recordings were at sites which produced discordant paresthesias., and their mean chronaxie time was 0.41ms. The remaining recordings were from sites producing concordant paresthesias, and these had a mean chronaxie time was 0.42ms. Both discordant sites had the highest rheobase currents, but there was no correlation between the rheobase current and the chronaxie time.

Table 1:Excitation Properties of Six Paresthesia Sites

Paresthesia Type	*Chronaxie Time (ms)*	*Rheobase Current (μA)*	*Refractory Period (ms)*
Discordant	0.57	14.4	n/a
Concordant	0.22	9.38	<0.21
Concordant	0.5	2.25	<0.21
Discordant	0.25	10.6	n/a
Concordant	0.51	2.45	n/a
Concordant	0.43	1.25	n/a

The frequency tuning curves of the six trials were analyzed by examining the percent increase in threshold between stimulation at 140Hz and 70Hz. The mean threshold increased by 93%, the median threshold increased by 67%, and one site exhibited no change in threshold. These data indicated that reducing the interpulse interval in the two-pulse experiment should lead to an increase in threshold when the second pulse fell within the refractory period of the action potential generated by the first pulse. Measurements at 2 sites yielded refractory periods that were less than 0.21 ms (the limit of the technique's discrimination).

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Discussion/Conclusions

Chronic electrical stimulation of deep brain structures (DBS) is being used to treat movement disorders in a number of neurological diseases and is also being explored for treatment of psychiatric disorders [1]. However, the mechanism(s) of action of DBS is unknown, and this lack of knowledge may limit improvements in the therapy and applications to new indications. A fundamental question related to the mechanisms of action of DBS is which neural elements (thalamocortical relay cells, thalamocortical interneurons, axons of passage) are affected by stimulation under different conditions. In this study the excitation characteristics of paresthesias produced by microstimulation of the human thalamus were measured to determine which neural elements are responsible for generating different types of paresthesias. The hypothesis was that concordant paresthesias are produced by activation of local neurons and would thus have longer chronaxie times than discordant paresthesias, presumed to arise from activation of axons of passage. The data revealed no differences between the chronaxie times of concordant and discordant paresthesias.

The hypothesis that concordant paresthesias have longer chronaxie times than discordant parasthesias rested on the presumption that cells have longer chronaxie times than axons. It is clear that the chronaxie time of cells activated intracellular is significantly longer than the chronaxie times for activation of axons, either intracellulary or extracellularly [5]. However, the chronaxie time of cells activated extracellularly may be very similar to the chronaxie time of axons activated extracellularly. Both modeling [6] and experimental [Nowak and Bullier] results demonstrated that with electrodes positioned over cells, action potential initiation actually takes place in the nodes of Ranvier of the axon distal to the cell body. As a result of axonal initiation during cellular stimulation, the chronaxie times measured with extracellular stimulation of CNS neurons are similar for electrodes positioned over the axon and electrodes positioned over the cell [5]. Therefore, even if concordant parasthesias are evoked by stimulation of local cells, their strength duration properties may reflect

those of axons. Further, the differences between chronaxie times for CNS cells excited by electrodes over the cell and over the axon are dependent on the electrode to neuron distance [6]. Thus, differences in chronaxie times measured with extracellular stimulation may not be sensitive enough to detect differences between activation of local cells and activation of axons of passage. Another possibility is that differences in chronaxie times represent activation of myelinated versus unmyelinated axons or axons of different caliber. Further modeling studies are required to determine and perhaps improve the sensitivity of chronaxie time as a measure of which neural elements are activated.

A persistent source of error in this study was variability the patients' responses to identical stimulation parameters over time. Many reasons may exist for this variability. The microelectrode may make minute movements during the testing protocol. If this were frequently the case, we would expect to find a greater percent deviation at sites with lower rheobase currents, as these are sites where the electrode is presumably closer to the stimulated element. No such correlation was found. Another possibility is that the patient's subjective threshold for reporting a paresthesia will change over time. To minimize this possibility we have attempted to alternate stimuli that we expect will evoke a paresthesia with stimuli that we expect will not evoke any response. However, we still found that the threshold drifted upwards in 7/13 units. Five of these units were excluded from out data set, in addition to 2 other units that had randomly varying thresholds. .

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