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Clinical and Experimental Aspects of Deep Brain Stimulation

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Abstract—**This presentation will review the effects of deep brain stimulation (DBS) for movement disorders in patients, and the cellular mechanisms that may explain these effects.**

I. Introduction

Deep brain stimulation (DBS) has revolutionized the treatment of several movement disorders, notably Parkinson's disease (PD) [1], dystonia [2], and tremor [3]. In addition its indications have recently been expanded for obsessive-compulsive disorder [4],[5], depression [6], epilepsy [7],[8], pain [9], cluster headache [10],[11], minimally conscious state [12], and even dementia [13]. Although the site of electrode implantation varies depending on the condition, the common feature of almost all DBS therapy is that the electrical pulses must be high frequency (>100 Hz) in order to be effective. Exactly how DBS works and its effects on neuronal functioning within the stimulated nucleus and downstream structures are the focus of this presentation.

I will briefly review the clinical use of DBS in thalamus for the treatment of tremor to illustrate some of the fundamental effects of DBS that must be explained by cellular models. Most of the presentation will be devoted to my lab's work on the underlying cellular effects of DBS and how these explain the clinical features. Finally the potential of therapeutic electrical stimulation will be discussed based on our present understanding of its mechanisms of action.

II. DBS for Essential Tremor

The key features of DBS for essential tremor (ET), a common movement disorder in which patients exhibit a postural or action-induced 3-8 Hz tremor, include the following. (i) The results of thalamic DBS is very similar to thalamotomy [3] or lesioning of the same thalamic nucleus [14]. (ii) The correct location of DBS placement (or lesioning) are critical for a good clinical outcome [15],[16]. (iii) Another characteristic that should be explained by the proposed mechanism of action and can be exploited in the experimental work, is the immediate benefit of thalamic DBS on tremor [17]. (iv) The effects of stimulation on tremor are frequency-dependent. (v) The final important attribute of thalamic DBS is that patients do not experience any involuntary movements or motor disruption with prolonged DBS [18].

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III. Mechanisms of Action

Recently there have been several publications that address the mechanisms of action of DBS. I will focus on the effects of simulated DBS in thalamocortical brain slices, first the local effects around the stimulated site, then the distant effects occurring at the cortical level.

A. Local effects

We found that high frequency stimulation produced depolarization of thalamic neurons in slice, and the effects were stimulation frequency and amplitude dependent [19]. Two types of neuronal responses to high frequency stimulation were observed [20]. Depolarization could be transient, occurring only at the onset of the stimulus train, or sustained throughout the train, and we referred to these responses as type 1 and 2, respectively. In both cases, depolarization was dependent on axonal activation and glutamatergic synaptic transmission. Blockers of action potentials, glutamate receptors and calcium all prevented somatic depolarization. While DBS did not seem to alter the steady state input resistance of the cells, it did reduce the threshold for action potential generation. We coined the terms "functional deafferentation" and "functional inactivation" to describe the effects of DBS on thalamic neurons. Functional deafferentation is the loss of synaptic input to post-synaptic thalamocortical neurons, as occurred in type 1 responses. Functional inactivation referred to type 2 responses, where spike inactivation was followed by repetitive spikes, while the cell remained depolarized, and which disrupted the rhythmic pattern of the outgoing signal. These mechanisms, driven primarily by synaptic activation, helped to explain the paradox that lesions, GABA receptor activation with muscimol [21] and DBS all effectively stop tremor.

Detailed study of type 1 responses, the transient responses induced by high frequency stimulation where depolarization occurred only at the onset of the stimulus train, revealed several important features [22]. During stimulation, neurons were incapable of firing action potentials or even displaying excitatory post-synaptic potentials (EPSPs). The cells were "functionally deafferented" during the stimulus train. Using the principle that two pulses applied 20-40 ms apart to the same axonal pathway will potentiate (increase the amplitude of the second EPSP), and two pulses applied to different pathways will not potentiate, we identified 2 inputs to 1 neuron in thalamic slices. Low frequency stimulation (5 Hz) mimicking afferent tremor input was applied through one electrode (electrode A) and high frequency stimulation (125 Hz) mimicking DBS, was then applied through the same electrode (A). During the simulated DBS train, EPSPs

elicited by the 5 Hz stimuli disappeared. DBS seemingly blocked the afferent input from the same pathway reaching the neuron under study. When the 5 Hz tremor-like input was applied with a separate electrode (B) to an independent pathway (B), high frequency DBS applied though electrode A, failed to alter EPSPs elicited through pathway B. This indicated that the suppression of tremor-like afferent activity was specific to the stimulated pathway and did not spill over to another pathway.

We concluded that DBS produced synaptic depression at the pre-synaptic level for the following reasons. When we applied cyclothiazide, which prevents AMPA receptor desensitization, to the slice, there was no change in the depolarizing effect of simulated DBS. The specificity of the neuronal response to single pathway stimulation and its rapid time course of depression made the possibility of an intracellular post-synaptic cascade very unlikely. DL-threo-beta-benzyloxyaspartate (DL-TBOA), a glutamate re-uptake inhibitor, also failed to alter the effect of DBS in our slice model, making non-specific extra-synaptic glutamate spillover highly improbable. Synaptic depression was limited to the homosynaptic pathway; -methyl-4-sulphonophenylglycine or MSPG, a non-selective antagonist of presynaptic metabotropic glutamate receptors, failed to alter responses; and finally, the rapid time course of recovery of homo-synaptic epsps after DBS was turned off, was in line with known recovery of the readily releasable pool of neurotransmitter [23].

The direct role of extracellular stimulation on neuronal soma was also investigated in the presence of glutamatergic blockade. We used whole cell patch clamp techniques to identify that simulated DBS in thalamic slice activated an I_h current, immediately at the onset of stimulation [22]. It failed, however, to inhibit both the persistent Na^+ current and the rebound potential related to I_T currents, which in thalamus are made up mainly of the low threshold Ca^{2+} current (LTS) responsible for the rebound bursts [24]. Regardless, such activation of I_h did not seem to be responsible for the synaptic depression induced by simulated DBS nor did it alter the synaptic responsiveness to other input.

B. Distant effects of DBS

Modeling studies suggested that the downstream projection sites from the nucleus in which DBS was applied may be more relevant to the mechanism of action than the local effects. Therefore we investigated the remote cortical effects of thalamocortical stimulation in slice.

The first question that must be addressed is the following: does the high frequency DBS signal applied to thalamocortical axons make it to the cortex? We first examined the ability of thalamocortical and corticothalamic neurons to follow stimuli applied to the internal capsule in sagittal rat brain slices [25]. After proving that we were antidromically activating the axon of the neuron under study, we applied 10-300 Hz stimulation to the capsule. Thalamocortical fibres failed to faithfully conduct action potentials at stimulation frequencies >50 Hz; however, complete conduction block did not occur.

The next stage of processing after the axon is the synapse. Therefore the next question we asked was whether high frequency stimulation of thalamocortical axons will affect downstream post-synaptic neurons in the cortex . Motor cortical neurons depolarized in response to subcortical external capsule stimulation in a frequency-dependent manner, however these depolarizations were not sustained. Intracortical inhibition was not responsible for the return to baseline membrane potential, as $GABA_{A/B}$ antagonists failed to sustain the DBS-induced depolarization. DBS also failed to alter firing rates in motor cortical neurons manually depolarized by intracellular current injection. Instead synaptic depression was likely responsible for the lack of sustained depolarization in response to high frequency stimulation. There was a marked depression of EPSP/Cs after the DBS train and its time course was dependent on the stimulus train length. The time course of recovery fit that described for depletion of the readily releasable pool of transmitter [26], [27]. Depression of post-synaptic currents with repetitive stimulation was not attributable to desensitization of AMPA receptors because cyclothiazide failed to alter responses to DBS. Synaptic depression was specific to the pathway stimulated. Stimulation of superficial cortical layers projecting to motor cortical neurons continued to produce EPSPs in pyramidal neurons during subcortical high frequency DBS.

To summarize, synaptic depression prevented sustained activation of cortical neurons in slice when high frequency stimulation was applied to subcortical white matter or thalamus. Axons failed to faithfully follow high frequency stimuli but did not undergo complete conduction block. These results are likely specific to the nuclei and pathway stimulated, and do not necessarily apply to other DBS sites used clinically. In fact, there is accumulating evidence that the properties of the neurons and axons close to where DBS is applied are critically important in determining the cellular response and thereby likely mechanisms involved.

IV. SUMMARY, FUNCTIONAL IMPLICATIONS AND POTENTIAL

The cellular mechanisms of DBS are related to frequency-dependent membrane depolarization, which in thalamus is synaptically mediated. Thalamic DBS does not alter intrinsic membrane currents (I_T, I_{Nap}) at physiologic potentials, but does have a small effect on I_h. In STN synaptic transmission likely also plays a role but there are more obvious direct effects of stimulation on membrane properties, such as the resurgent Na^+ current [28]. Neurons are either functionally deafferentated, unable to fire action potentials due to synaptic depression, or inactivated, abnormal firing patterns are masked by an artificial firing pattern [29]. The effects are specific to the pathway stimulated so that functional deafferentation can limit propagation of pathophysiological tremor signals without disrupting information from other pathways.

Thalamic stimulation despite seemingly activating thalamocortical axons projecting to the motor cortex, does not disrupt motor control. Synaptic depression and axonal filtering prevent remote cortical excitation during high frequency subcortical DBS. Spontaneous cortical firing is

not altered, as the synaptic depression is specific to the stimulated pathway, alone.

Our *in vitro* data may explain many of the clinical features important for thalamic DBS in patients. The similarity of thalamic DBS to thalamotomy is likely due to functional deafferentation. Tremor cells are unable to propogate EPSPs or action potentials and thereby the tremor signal does not make it to the motor output level. Functional deafferentation occurs immediately upon application of DBS and is rapidly reversible. DBS is site-specific both clinically in patients with tremor and in the slice model. The cellular effects of stimulation are frequency-dependent, with high frequencies (>60 Hz) required for tremor suppression. Finally patients do not experience any involuntary movements or motor disruption with prolonged DBS. Axonal filtering at the level of thalamocortical axons and synaptic depression in the motor cortex prevent such disruption. The effects are specific to the pathway stimulated and do not spill over to other pathways in thalamus or cortex.

While much of the data discussed here is specific to thalamic and subcortical white matter DBS, there are some important principles that can be broadly applied to many forms of nervous system electrical stimulation. No matter where the stimulating electrode is placed, the effect of extracellular stimulation will be axonal/dendritic fiber excitation [30]. However, the effect of axonal activation on post-synaptic cellular activity will depend on the ability of axons and synapses to transmit the signal. If the stimulation is low frequency (<50 Hz), then axons and synapses should convey the signal with high fidelity. However, if the stimulation is high frequency (>100 Hz), conduction failure and transmitter depletion may filter out the high frequency signal. Effects are pathway specific and do not spill-over to non-stimulated tracts.

This frequency dependent effect of electrical stimulation on specific axons and terminals has tremendous potential. The mainstay of treatment for neurologic and psychiatric conditions at this point is medication. Many of these drugs replace or alter neurotransmitter release, re-uptake or receptors. Drugs work fairly indiscriminately at all similar nervous system synapses and they cannot be timed to work only when symptoms require. As a result, medications often produce multiple and unacceptable side effects. DBS has the capability to selectively alter neurotransmitter release in a specific pathway and in a controlled manner, as required by symptoms. The cost of introducing a new drug to the market are ever increasing and are limiting new drug development. The costs of electrical stimulation are inexpensive, in comparison. With an understanding of how DBS works at the cellular level, the full potential of electrical neuromodulation may become realized. With knowledge of the anatomy and physiology of axonal projections and neuronal properties we may be able to predict benefits and side effects of this technology in other pathways and apply it rationally for new indications.

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