

Mechanisms of Deep Brain Stimulation: Implications for Physiology, Pathophysiology and Future Therapies

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Abstract

Despite the efficacy of deep brain stimulation (DBS) for an expanding range of neurological and psychiatric disorders little is known about its mechanisms of action. We report results from microelectrode recordings in the motor cortex (mCtx), sensory cortex (sCtx), globus pallidus externa (GPe) and interna (GPi), and putamen (Pt) in non-human primates during stimulation of the subthalamic nucleus (STN) in a manner analogous to human DBS. We stimulated with different frequencies of regular stimulation and with pair-pulses to demonstrate resonance effects. The latter are manifest as increase probability of neuronal discharge to the second pulse as a function of the time interval from the first pulse. The results demonstrate the DBS activates neurons in the basal ganglia-thalamic-cortical (BG-Th-Ctx) system. Responses consist of antidromic activation in mCtx and GPe and short latency oligosynaptic activations. There is no difference in the direct effect (first 8 ms) regardless of stimulation frequency (130 pulses per sec [pps], 100 pps or 50 pps). Paired-pulse stimulation demonstrates resonance effects at short inter-stimulus pulse intervals suggestive of high frequency reentrant oscillators and consistent with previous demonstration of multiple and high simultaneous periodic activity in neuronal spike trains in the BG-Th-Ctx system. The implications of these findings for theories of physiology and pathophysiology are discussed.

1. INTRODUCTION

Deep Brain Stimulation (DBS) is increasingly important therapy for an expanding array of chronic neurological and psychiatric disorders. For Parkinson's disease, DBS is effective for patients in whom pharmacological agents ¹, ablation and even brain transplantation have

failed (patients have developed "run away" dyskinesia that required DBS) ². Despite the efficacy of DBS, there is no clear understanding of its mechanisms of action. Consequently, a better understanding of DBS could lead to more and better treatments for a host of neurological disorders. Further, DBS must be addressing important pathophysiological mechanisms and quite likely normal physiology as well.

2. METHODS

We completed a series of experiments utilizing stimulation of the subthalamic nucleus (STN) of non-human primates in a manner analogous to DBS in humans while conducting microelectrode recordings of extra-cellular action potentials in motor cortex (mCtx), sensory cortex (sCtx), putamen (Pt), caudate nucleus (Cn), globus pallidus interna (GPi) and globus pallidus externa (GPe). We utilized continuous regular stimulation at different frequencies and a paired-pulse regimen to study the dynamics of the basal ganglia-thalamic-cortical (BG-Th-Ctx) system.

3. RESULTS

1. DBS in the vicinity of the STN results in antidromic activation of neurons in the mCtx (~2 ms) and GPe (~2ms). This is consistent with activation of axons projecting to or in the vicinity of the STN.
2. DBS in the vicinity of the STN results in short latency oligosynaptic activation of neurons in the mCtx (~5 ms), sCtx (~4 ms), GPi (~5ms), Pt (~5.5 ms), and GPe (~6 ms). It is possible that these later responses in sCtx, GPe, GPi and Pt represent propagation of the antidromic activations of mCtx to the sCtx and through the BG-Th-Ctx system. Activation of GPi could result from stimulation of the STN output neurons to GPi. This is strong evidence that STN DBS does not inhibit the STN output. These observations suggest that previous

demonstrations of much slower conduction times, particularly in the cortico-striatal pathways are in error³.

3. There is very little difference in the responses to STN DBS in the first 8 ms to DBS at 130 pulses, 100, or 50 pps. This is strong evidence against the notion that different DBS frequencies have different direct effects. Namely, high frequency DBS does not cause inhibition while low frequency DBS causes activation.
4. After the initial 8 ms response to the DBS pulse, the neuronal activity appears to return to baseline. Thus, high frequency DBS may suppress baseline activity by not allowing sufficient time subsequent to each DBS pulse for the neuron to return to baseline activity. In the case of disease, the high frequency stimulation prevents the return to pathological neuronal activity. Alternatively, high frequency stimulation may drive the BG -Th-Ctx system to regularity, thereby reducing the misinformation content pathological system.
5. Paired-pulse stimulation allows demonstration of resonance effects (increased probability of neuronal discharge) when the second stimulation of the pair is given when the effects of the first pulse have traversed the system. The time period between the pair of pulses associated with the resonance effect is the measure of the time required to traverse the system or the fundamental frequency of the reentrant oscillator that comprises the system. All neurons recorded in the BG-Th-Ctx system demonstrated multiple and high frequency resonance effects that could not be explained solely on membrane dynamics associated with post-action potential conductance changes. Several neurons demonstrated harmonic effects consistent with propagation through a reentrant oscillator. These observations are consistent with demonstration that all neurons in the BG-Th-Ctx demonstrate multiple and high frequency periodic activity in their neuronal spike train during baseline activity⁴.

4. DISCUSSION AND CONCLUSIONS

1. DBS does not inhibit the target structure. This has been confirmed by large body of evidence including microelectrode recordings in animals and humans⁵⁻⁷, regional cerebral blood flow studies using PET⁸, and neurotransmitter studies^{9,10}. A explanation based on mathematical modeling has been provided¹¹.
2. Therapeutic STN DBS increases activity in the GPi. Consequently, increased activity in the GPi cannot be causally related to the pathophysiology of Parkinson's disease contrary to current theory^{12,13}. Rather, the demonstrations of increased GPi activity in animal models of parkinsonism and in human recordings is epiphenomenal.
3. The effects of STN DBS are propagated throughout the BG-Th-Ctx suggesting that the therapeutic effects are a systems phenomena as opposed to a single (or few) structure. This hypothesis is consistent with the observation DBS applied to a number of structures in BG-Th-Ctx is therapeutic including the GPi¹, ventrolateral thalamus¹⁴, mCtx¹⁵, STN¹, and GPe¹⁶. Thus, the system or network can be activated via a number of input points.
4. If DBS exerts its anti-pathophysiological (therapeutic) effect through the system, then could not the pathophysiological mechanism be systems-based¹⁷?
5. Alternative theories of pathophysiology include: abnormalities in dynamic mechanisms related to behavior not manifest in baseline discharge rate¹⁸ and changes in the pattern rather than rate^{7,19}.
6. Additional alternatives include overwriting of misinformation to no by driving BG-Th-Ctx activity to high frequency and regular activity²⁰. Preliminary studies in non-human primates performing a behavioral task demonstrates that some neurons in the BG-Th-Ctx system that normally modulate their discharge rates with behavior fail to do so with high frequency STN DBS while continuing to modulate their activity with lower frequency DBS. This theory represents a significant departure from previous concepts of pathophysiology characterized by one-dimensional push-pull systems of excitation and inhibition^{12,13}. Pathophysiology may have more to do with misinformation rather than loss of a specific neurotransmitter. An analogy would be a "run time" error in computer programming in otherwise intact computer systems.
7. Demonstration that the BG-Th-Ctx system can best be described as a large set of non-linear reentrant oscillators loosely

embedded in scale-free networks greatly expands the range of normal and pathophysiological mechanisms and properties¹⁷. The striking analogy to mathematical²¹ and physical systems means that mechanisms and properties for these systems may be translated into neurophysiological mechanisms and properties. This could be the basis for a new theoretical systems neuroscience and engineering. Further, these implications might apply to any brain system that can be characterized as reentrant oscillators including the limbic system and the thalamo-cortical systems.

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