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New Insights Into the Mechanisms Underlying Efficacious Deep Brain Stimulation

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In this issue of *Mayo Clinic Proceedings*, Chang and an international team of collaborators—collectively representing departments of neurosurgery, physiology and biomedical engineering, and engineering at Mayo Clinic in Rochester, Minnesota; Hanyang University in Seoul, South Korea; Soonchunhyang University in Bucheon, South Korea; Illinois State University in Normal, Illinois; and the University of Memphis in Memphis, Tennessee—present a fascinating and important novel discovery that offers insights into how deep brain stimulation (DBS) may work at the cellular level.[1] Deep brain stimulation is a technique whereby minute electrical pulses, delivered to highly specific brain regions, are administered to provide a desired effect on brain function.

First approved for use in the United States in 1997 by the US Food and Drug Administration, DBS is commonly utilized for the management of numerous neurologic conditions including essential tremor, tremors associated with Parkinson disease, and dystonia.[2,3] Outside the approved indications, DBS has also been used to treat cluster headache, short-lasting unilateral neuralgiform headache with conjuntival injection and tearing, Meige syndrome (a condition characterized by facial dystonia and tics), orthostatic tremor, chronic pain, memory loss from Alzheimer disease, epilepsy, Tourette syndrome, depression, and obsessive-compulsive disorder.[1-4] The general concept for DBS treatment is to implant an electrode in a specific target in the brain where stimulation will ameliorate the disease-state symptoms without producing adverse effects. For example, the ventral intermediate nucleus of the thalamus (VIM) is targeted in essential tremor and sometimes for severe parkinsonian tremor, whereas the subthalamic nucleus (or globus pallidus internus) is targeted for dystonia or Parkinson disease tremor.[1-3]

Deep brain stimulation has helped tens of thousands of patients worldwide by attenuating symptoms, but it does not provide a cure for the underlying disease state. Nevertheless, the effectiveness of DBS in reducing the symptoms and improving the quality of life for patients with these disorders has made this treatment popular among patients and clinicians.

Despite its popularity, the mechanisms by which DBS ameliorates symptoms are poorly understood.[1-4] It is postulated that DBS exerts its effect through modulation of neural activity, by stimulating or inhibiting neurons and fiber pathways that subsequently increase or decrease specific neurochemical release. During DBS for essential tremor, for example, it is commonly observed that simply implanting an electrode into a specific target in the thalamus can result in immediate reduction of the tremor before any exogenous electrical stimulation is begun. This effect is known as the *microthalamotomy effect* and has been reported in up to 53% of patients undergoing the brain stimulation procedure for tremor.[1-3] This microthalamotomy effect is considered a scientific curiosity by those involved in DBS procedures, but the mechanism responsible for this effect and the potential importance toward a better understanding of how DBS may work have not been studied previously.

In their analysis, Chang et al[1] performed real-time fast-scan cyclic voltammetry to quantify neurotransmitter concentrations in microscopic brain regions for the first time in human subjects, and they obtained real-time recordings of neurochemical changes at the time of DBS implantation. Fast-scan cyclic voltammetry is a technique whereby particular chemical compounds can be identified by their specific electrochemical characteristics (ie, voltage measurements). The observed neurochemical changes in the study by Chang et al were correlated with the microthalamotomy effect and clinical observation of tremor reduction in 7 patients being treated for benign essential tremor. The implantation of the DBS electrodes evoked a large increase in the oxidation voltage detected in all 7 patients, with a peak current at $+1.45 \pm 0.03$ V[1]; a smaller oxidation current peak at $+1.19 \pm 0.06$ V was observed in 4 of 7 patients.[1] Postcalibration of the flow cell analyses demonstrated that the 2 oxidation current peaks matched those for adenosine and its oxidation by-products.

Adenosine release induced by electrode implantation was verified using an in vitro pharmacological test that employed rat brain slices. The collective data suggested that the implantation of a DBS electrode in the VIM evokes a local release of adenosine and other biologically active compounds and ions at the time that a microthalamotomy effect is observed clinically.[1]

Chang and colleagues introduce the compelling and fascinating concept that implantation of a DBS electrode in the VIM causes a neurochemical change of adenosine release that may be responsible for tremor reduction in patients with essential tremor. The role of adenosine in patients with tremor has been studied using other techniques,[1-3] and, as the authors themselves stated in their article, the previous data on this topic are conflicting. Nevertheless, the data presented in this analysis using elegant and novel techniques provide new insight into the potential mechanism of action of DBS. These findings are important because such knowledge may eventually lead to future neuromodulation techniques that utilize an infusion of appropriate chemicals to modulate the electrical stimulation.

Certainly, there are many questions regarding DBS that remain unanswered by this study. However, this novel technique of in vivo fast-scan cyclic voltammetry introduced by Chang et al will likely continue to lead to further insights and understanding of the mechanisms of action of DBS. Deep brain stimulation likely exerts its effects not just locally but also distally or system-wide through activation or inhibition of fiber pathways.[1-3] What role, if any, that adenosine plays in the system-wide effects are unknown and would need to be accounted for in any global model explaining the mechanistic aspects of DBS.

We speculate that the research of Chang et al is also germane to other conditions outside of movement disorders. As noted, DBS is being utilized in trials worldwide for a variety of neurologic and psychiatric conditions. In all of the conditions in which some benefit has been reported, the fundamental mechanism by which DBS improves the symptoms of the condition is unknown.[1-4] Could other beneficial neurochemical modulation, with the exact chemical(s) being released dependent on the location of the stimulating electrode, be observed by the simple act of implanting an electrode? Might this explain the efficacy of DBS in a number of apparently disparate neurologic conditions?

Some clues to the answer come from the field of epilepsy. In 2001, Katariwala and colleagues[5] from Emory University School of Medicine reported that patients who had undergone placement of temporary (ie, left in place from 1 to 21 days) intracerebral and/or subdural intracranial electroencephalography and electrocorticography electrodes subsequently had cessation of their seizures without any surgical resection, and this effect lasted anywhere from 11 months to 15 years after transient implantation of such electrodes. The study of Chang et al prompts us to consider whether such a mechanical stimulus can provoke long-term changes in neurologic function simply because an individual patient's neurochemistry is altered by mechanical stimulation of brain tissues. Therefore, this study could have important implications in that the technique utilized to find the adenosine release in vivo may be applied to other conditions. As the applications of DBS continue to expand, understanding how such a technique works may prove to be quite useful in elucidating future approaches to dealing with difficult, stigmatizing chronic neuropsychiatric conditions. Thus, these results may open the doors to finally restoring quality of life for the many who suffer from these various maladies.

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REFERENCES

1. Chang S-Y, Kim I, Marsh MP, et al. Wireless fast-scan cyclic voltammetry to monitor adenosine in patients with essential tremor during deep brain stimulation. *Mayo Clin Proc*. 2012; 87(8):760-765.
2. Lyons MK. Deep brain stimulation: current and future clinical applications. *Mayo Clin Proc*. 2011;86(7):662-672.
3. Hu W, Klassen BT, Stead M. Surgery for movement disorders. *J Neurosurg Sci*. 2011;55(4):305-317.
4. Fisher RS. Therapeutic devices for epilepsy. *Ann Neurol*. 2012; 71(2);157-168.
5. Katariwala NM, Bakay RA, Pennell BP, Olson LD, Henry TR, Epstein CM. Remission of intractable partial epilepsy following implantation of intracranial electrodes. *Neurology*. 2001;57(8); 1505-1507.