OPINION

Deep Brain Stimulation (DBS) and their clinical application

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ABSTRACT

Deep Brain Stimulation (DBS) has developed during the past 20 years as a remarkable treatment option for several different disorders. Deep Brain Stimulation (DBS) has provided remarkable benefits for people with a variety of neurologic conditions. The clinical use of Deep Brain Stimulation (DBS) is among the most important advances in the clinical neurosciences in the past two decades. As a surgical tool, DBS can directly measure pathological brain activity and can deliver adjustable stimulation for therapeutic effect in neurological and psychiatric disorders correlated with dysfunctional circuitry. Deep Brain Stimulation (DBS) is a surgery to implant a device that sends electrical signals to brain areas responsible for body movement. Electrodes are placed deep in the brain and are connected to a stimulator device. Similar to a heart pacemaker, a neurostimulator uses electric pulses to regulate brain activity. DBS can help reduce the symptoms of tremor, slowness, stiffness, and walking problems caused by Parkinson's disease, dystonia, or essential tremor. Successful DBS allows people to potentially reduce their medications and improve their quality of life. The development of DBS has opened new opportunities to access and interrogate malfunctioning brain circuits and to test the therapeutic potential of regulating the output of these circuits in a broad range of disorders. This review summarizes many of the current and potential future clinical applications of this technology and complications of DBS. pharmacological interventions. Single analgesic therapies may be limited in their ability to comprehensively target these complex pain signaling pathways. Therapeutic approaches acting on multiple pain transmission pathways through different mechanisms of action provide an opportunity to maximize efficacy and tolerability in the treatment of pain.

Key Words: *DBS, Headache; Movement disorders; Parkinson disease; Dystonia, Tremor*

INTRODUCTION

Deep Brain Stimulation (DBS) has provided dramatic clinical benefit for people with Essential Tremor (ET) and Parkinson Dise-ase (PD). Placement of high frequency stimulating electrodes in the region of the ventral intermediate nucleus of the thalamus (VIM) can markedly reduce tremor in these conditions, and stimulation of either the Subthalamic Nucleus (STN) or the internal segment of the globus pallidus (GPi) may not only reduce tremor, but also decrease bradykinesia, rigidity, and gait impairment that plague people with PD. Furthermore, many have touted the potential benefit of DBS of selected brain regions for other movement disorders such as dystonia or Tourette syndrome, as well as a variety of disorders such as pain, depression, and Obsessive Compulsive Disorder (OCD). Despite these realized and potential advances in treatment, controversy swirls around a number of clinically relevant and basic mechanistic issues. What conditions are amenable to treatment by DBS? What are the mechanisms of action of DBS? What effect does DBS have on the function of brain circuits? We address these controversial issues and emphasize the need for future investigations. To set the stage, however, we first review the history of the development of DBS as a therapeutic tool.

Deep brain stimulation is an established treatment for people with movement disorders, such as essential tremor, Parkinson's disease and dystonia, and psychiatric conditions, such as obsessive-compulsive disorder. It's also approved for use by the Food and Drug Administration to reduce seizures in difficult-to-treat epilepsy. This treatment is reserved for people whose symptoms aren't controlled with medications.

Ever since classical demonstration of the localized electrical excitability of the motor cortex, electrical stimulation of the brain has played a major role in investigations of brain function. The first report of human cortical stimulation appeared four years later. Although electrical stimulation was used to map cortical function in the 1930s, it was not until human stereotaxic devices were developed that neurosurgeons could begin to investigate the effects of stimulating deeper structures. By the early 1950s, intraoperative stimulation was used to identify deep structures such as the corticospinal tract prior to

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lesioning the globus pallidus or thalamus. Most reports in the 1950s focused on positive phenomena that were elicited bystimulation. In the early 1960s, it was reported that high-frequency (100-Hz) stimulation of the ventrolateral thalamus could diminish tremor. The idea of treating neurologic disorders with chronic stimulation began to emerge in the 1960s, but stimulation was largely used for targeting surgical lesions developed a method of implanting a bundle of multiple electrode wires deep in the brain and leaving them in place for weeks, during which stimulation could be delivered. The goal of the stimulation was to delineate the "best" target for a subsequent lesion. With the implanted wires, a lesion could be made in small steps over a span of days to weeks to try to achieve maximum benefit without untoward effects. Although the goal was still lesion guidance, this is perhaps the earliest report of stimulation through chronically implanted electrodes. In the early 1970s, reports of using chronic stimulation therapeutically emerged for treating pain, movement disorders, or epilepsy published the first large series of chronic cerebellar stimulation studies for cerebral palsy. In those cases, stimulation was delivered transcutaneously through inductive coupling devices to electrodes implanted on the surface of the cerebellar cortex. Benefit was said to occur in 49 patients of 50 patients. However, cerebellar stimulation in cerebral palsy eventually fell out of favor when blinded studies failed to show consistent benefits. By 1980, other reports of treating movement disorders with chronic stimulation had appeared. Although the first long-term internally implanted cardiac pacemaker was developed by 1960, it was not until the 1990s that implantable pacemaker technology was combined with chronically implanted deep brain electrodes for long-term chronic DBS 14. Since then, DBS has become increasingly used for treating a variety of disorders. These are summarized briefly in the section below. The scope of DBS is rapidly expanding and parallels our increasing understanding of the nature of brain circuit dysfunction In order to take stock of the field, this Review addresses the status of DBS by highlighting its current challenges and future. We begin by reviewing the putative mechanisms of DBS and its effects on neural tissue and networks, followed by an overview of how preclinical models have informed translational applications. We then provide an overview of the spectrum of clinical applications, from motor to non-motor, including the challenges for both widely used and emerging indications. Finally, we conclude by examining the clinical, technical and ethical challenges that will help to inform future directions of the field. At the cellular level, the opening of sodium channels can generate an action potential, which typically initiates in the axon. Stimulation-induced action potentials then propagate in both the orthodromic and antidromic directions to the axon terminals of the neuron. Under the typical conditions of DBS, many axons will be stimulated. The stimulated axons are capable of following stimulation frequencies at ~100 Hz with very high fidelity, but synaptic transmission of these high-frequency signals is a far less robust and much more complicated process than that of axonal transmission. Axon terminals can exhaust their readily releasable pool of neurotransmitters and postsynaptic receptors can depress under such high-frequency activity. Even if these synapses remain functional during DBS, information processing theories dictate that they will become low-pass filters that suppress transmission of low-frequency signals. This general phenomenon, known as 'synaptic filtering', could have a key role in DBS, whereby the neurons and connections that are directly stimulated by DBS hinder the propagation of oscillatory activity patterns within their associated brain networks. The basic biophysical effects of DBS provide a context in which to begin to interpret the network activity patterns that are observed in patients. As stimulation frequency remains constant during DBS, the information content of the stimulation signal is effectively zero, which could generate what is known as an 'information lesion' in stimulated neurons. Under this hypothesis, DBS-induced action potentials effectively override any intrinsic activity in the directly stimulated neurons and thereby limit the propagation of oscillatory activity through the network. In addition, the basic concepts of information lesion and synaptic filtering might work in concert to generate robust suppression of low-frequency signals in stimulated brain circuits. However, not all data support the hypothesis that high-frequency DBS introduces a simple information lesion. Studies in awake and behaving primates have provided some evidence that physiological sensorimotor-related discharge in the pallidum might be maintained at least partially during STN or pallidal DBS. These studies suggest that DBS might act as a filter that permits some sensorimotor-related modulation of the activity of neurons in the stimulated area while selectively blocking transmission of pathological low-frequency oscillations. Likewise, other basal ganglia functions such as motor sequence learning or reward-based decision-making can be preserved during DBS of the STN or globus pallidus

CONCLUSION

DBS is an effective surgical treatment for movement disorders (Parkinson's disease, essential tremors and dystonia). It requires insertion of small electrodes to the deep brain targets and it is minimally invasive. The requirement for a high degree of accuracy and precision makes it a complication-prone procedure. Most of the complications are avoidable after a long learning curve. A dedicated movement disorder team comprising neurologists, neurophysiologists, functional neurosurgeons, neuropsychologists and nursing specialists is essential.