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The mechanisms of action of deep brain stimulation and ideas for the future development

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ABSTRACT

Deep brain stimulation (DBS) has been used as a treatment of movement disorders such as Parkinson's disease, dystonia, and essential tremor for over twenty years, and is a promising treatment for depression and epilepsy. However, the exact mechanisms of action of DBS are still uncertain, although different theories have emerged. This review summarizes the current understanding in this field. Different modalities used to investigate DBS such as electrophysiological, imaging and biochemical studies have revealed different mechanisms of DBS. The mechanisms may also be different depending on the structure targeted, the disease condition or the animal model employed. DBS may inhibit the target neuronal networks but activate the efferent axons. It may suppress pathological rhythms or impose new rhythms associated with beneficial effects, and involves neuronal networks with widespread connections. Different neurotransmitter systems such as dopamine and GABA upregulation are involved in the effects of DBS. There are also technical advances to prolong the battery life and specific targeting based on new electrode designs with multiple contacts which have the ability to steer the current toward a specific direction. There is ongoing work in closed loop or adaptive DBS using neural oscillations to provide the feedback signals. These oscillations need to be better characterized in a wide variety of clinical settings in future studies. Individualization of DBS parameters based on neural oscillations may optimize the clinical benefits of DBS.

Contents

Abbreviations: ACC, anterior cingulate cortex; ATP, adenosine triphosphate; BOLD, blood-oxygen level dependent; BG, basal ganglia; CBF, cerebral blood flow; Cg25, subgenual cingulate area (Brodmann) 25; cGMP, cyclic guanosine monophosphate; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; DOPA, dihydroxy phenylalanine; EEG, electroencephalography; FDA, food and drug administration; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; GABA, gamma amino butyric acid; GPe, globus pallidus externus; GPi, globus pallidus internus; HFS, high frequency stimulation; ISI, inter stimulus interval; ICN, inferior caudate nucleus; LAI, long latency afferent inhibition; LFP, local field potential; LID, levodopa induced dyskinesia; LTD, long term depression; LTP, long term potentiation; M1, primary motor cortex; MEG, magneto-encephalography; MEP, motor evoked potential; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine; NMDA, N-methyl D-aspartate; 6-OHDA, 6-hydroxydopamine; OCD, obsessive-compulsive disorder; PAS, paired associative stimulation; PD, Parkinson's disease; PDRP, PD-related metabolic pattern; PDTP, PD tremor-related metabolic pattern; PET, positron emission tomography; PPN, pedunculopontine nucleus; SAI, short latency afferent inhibition; SICI, short interval intracortical inhibition; SMA, supplementary motor area; SNpc, substantia nigra pars compacta; SNr, substantia nigra reticulata; SPECT, single photon emission computerized tomography; STN, subthalamic nucleus; TH, tyrosine hydroxylase; TMS, transcranial magnetic stimulation; UPDRS, unified Parkinson's disease rating scale; Vim, Ventro-intermedius nucleus of thalamus.

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1. Introduction to deep brain stimulation

1.1. Historical aspects

For centuries, electrical stimulation of the nervous system has been used as a treatment in many disorders including headache, depression and epilepsy (Schwalb and Hamani, 2008). In the Egyptian era, electrical shocks produced by eel were used to relieve pain. Other procedures such as electrocution of head and piercing the brain have been tried to abort symptoms of neurological and psychiatric disorders (Vilensky and Gilman, 2002; Cooper, 1973). With the advent of the stereotactic frame (Spiegel et al., 1947), selective ablative procedures such as thalamotomies and pallidotomies for movement disorders became popular. It was during these procedures that high-frequency stimulation of the targets produced clinical effects similar to the ablation itself (Ohye et al., 1964). Studies performed during a series of ablative procedures (Hassler et al., 1960) found that low frequency stimulation (4–8 Hz, occasionally 25 Hz) of the pallidum elicited tremors whereas high frequency stimulation (25–100 Hz) abolished tremors in Parkinsonian patients. These surgeries became much less popular with the advent of effective medical therapies with the introduction of levodopa in 1969 (Cotzias et al., 1969). However, with emergence of the complications of long-term levodopa treatment such as motor fluctuations and levodopa-induced dyskinesias (LID), coupled with advances in stereotactic surgery, led to a resurgence of surgical treatment for movement disorders. In contrast to the permanent effects of ablation, the adverse effects produced by deep brain stimulation (DBS) are generally reversible once the stimulation is turned off. Thus, DBS was proposed to offer a safer and more effective alternative to ablation and began to be used in the management of movement disorders (Benabid et al., 1987). The initial targets were the thalamus for tremor, and the pallidum and subthalamic nucleus (STN) for Parkinson's disease (PD).

1.2. Disorders treated with DBS

Although many disorders (Table 1) are being treated with DBS, in this review we will focus on movement disorders: PD, essential tremor and dystonia. We will briefly mention epilepsy and psychiatric disorders including depression and obsessive-compulsive disorder (OCD). The Food and Drug Administration (FDA) approved DBS as treatment for some of these disorders.

1.2.1. Parkinson's disease

PD is the commonest disorders treated with DBS. PD is a movement disorder characterized by the cardinal symptoms of tremor, rigidity, bradykinesia and postural abnormalities (Lang and Lozano, 1998). The prevalence of PD has been estimated to be 15% for people in 6th decade of life, and increases by 15–20% for each decade of life thereafter (Bennett et al., 1996).

1.2.1.1. Pathophysiology of PD. The use of stereotactic surgery for PD was driven by advances in the understanding of the pathophysiology and availability of animal models for PD. A prominent model to explain the pathophysiology of PD is the "rate model" based on changes in basal ganglia (BG) firing rates observed in animal models such as the 6-hydroxydopamine (6-OHDA) mouse and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model. These models consistently showed increased firing rate in the globus pallidus internus (GPi) and the subthalamic nucleus (STN) of the BG. These increased activities were due to degeneration of dopaminergic nigrostrial neurons which in turn modulates the projection of striatal medium spiny neurons to the direct and indirect pathways as proposed by Delong and colleagues (Delong, 1990). Thus, the changes in the activities of the direct and indirect pathways are thought to cause changes in firing neuronal firing rates in the GPi and STN (Figs. 1 and 2). It has been proposed that if the balance between these two pathways is