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Review article

Subthalamic nucleus deep brain stimulation on motor-symptoms of Parkinson's disease: Focus on neurochemistry

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ABSTRACT

Deep brain stimulation (DBS) has become a standard therapy for Parkinson's disease (PD) and it is also currently under investigation for other neurological and psychiatric disorders. Although many scientific, clinical and ethical issues are still unresolved, DBS delivered into the subthalamic nucleus (STN) has improved the quality of life of several thousands of patients.

The mechanisms underlying STN-DBS have been debated extensively in several reviews; less investigated are the biochemical consequences, which are still under scrutiny. Crucial and only partially understood, for instance, are the complex interplays occurring between STN-DBS and levodopa (LD)-centred therapy in the post-surgery follow-up.

The main goal of this review is to address the question of whether an improved motor control, based on STN-DBS therapy, is also achieved through the additional modulation of other neurotransmitters, such as noradrenaline (NA) and serotonin (5-HT). A critical issue is to understand not only acute DBS-mediated effects, but also chronic changes, such as those involving cyclic nucleotides, capable of modulating circuit plasticity.

The present article will discuss the neurochemical changes promoted by STN-DBS and will document the main results obtained in microdialysis studies. Furthermore, we will also examine the preliminary achievements of voltammetry applied to humans, and discuss new hypothetical investigational routes, taking into account novel players such as glia, or subcortical regions such as the pedunculopontine (PPN) area.

Our further understanding of specific changes in brain chemistry promoted by STN-DBS would further disseminate its utilisation, at any stage of disease, avoiding an irreversible lesioning approach.

Contents

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino) tetralin; HFS, high-frequency stimulation; ACh, acetylcholine; BDNF, brain derived neurotrophic factor; BG, basal ganglia; CSF, cerebro-spinal fluid; DA, dopamine; DAT, dopamine transporter; DAWS, dopamine-agonist withdrawal syndrome; DBS, deep brain stimulation; DOPAC, 3,4-dihidroxyphenylacetic acid; DR, dopamine receptor; EMG, electromyography; F-dopa, (18)F-fluorodopa; GPe, esternal globus pallidus; GPi, internal globus pallidus; HVA, homovanillic acid; iMAO, monoaminooxidase inhibitor; LC, locus coeruleus; LD, levodopa; LFS, low frequency stimulation; LID, levodopa-induced dyskinesia; LTD, long-term depression; LTP, long-term potentiation; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSN, medium spiny neurons; NA, noradrenaline; NAcc, nucleus accumbens; NO, nitric oxide; PD, Parkinson's disease; PDE, phosphodiesterase; PET, positron emission tomography; PPN, pedunculopontine nucleus; sGC, soluble guanylate cyclase; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SPECT, single-photon emission computed tomography; STN, subthalamic nucleus; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; UPDRS, unified Parkinson's disease rating scale; VA, ventral anterior nucleus; VEGF, vascular endothelial growth factor.

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Premise on the organization of the manuscript

Our manuscript addresses the major neurochemical changes induced by subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson's disease (PD) patients. This manuscript moves from the hypothesis that STN-DBS provides additional benefits to dopamine (DA)-mediated effects and possibly restores some degree of neuro-plasticity. Yet, available data from PD patients are still partial and, frequently, evidence collected from experimental disease models are not translated into meaningful messages for therapy. The need for updated results is even more urgent nowadays, as far as new DBS approaches, such as the adaptive one, promise to tailor stimulation protocols to different PD clinical states, determined by specific biochemical traits.

- In chapter 1, we briefly review some historical fundamentals, trying to evaluate to what extent stereotactic neurosurgery acts in synergy with DArgic drug treatments.

- Chapters 2 and 3 investigate the specific impact of STN-DBS on endogenous transmitters in basal ganglia (BG), examining DA, noradrenaline (NA), serotonin (5-HT), endogenous amino acids, but extending the analysis to non-conventional agents such as endogenous nucleotides.

- Chapter 4 examines new emerging scenarios that go beyond BG *strictu sensu* such as the cortical and subcortical circuitries, the putative involvement of glia and the role of pedunculopontine (PPN) region.

What does deep brain stimulation add to pharmacological therapy in PD?

1.1. Parkinson's disease therapy: the endless cycle of surgical and medical therapy

Nowadays, DBS represents a successful surgical treatment for Parkinson's disease (PD). In support of the crucial role played by the subthalamic nucleus (STN) in the pathophysiology of PD (Bergman et al., 1994; Wichmann and DeLong, 2003, 2003), the electrical stimulation of STN has been proven to improve motor function (Deuschl et al., 2006; Rodriguez-Oroz et al., 2005) and the quality of life of PD patients in moderate-advanced stages. Recently, this surgical approach was advocated as soon as the first motor fluctuations appear (deSouza et al., 2013, 2015; Deuschl et al., 2013; Schuepbach et al., 2013; Woopen et al., 2013; Youngerman et al., 2016). Further, some reports have indicated, albeit in a small cohort, that STN-DBS may contribute to restoring plasticity (Kim et al., 2015a; Udupa et al., 2015).

High-frequency stimulation (HFS) represents an alternative to ablative surgery, on the basis of reversibility. However, lesioning is still performed in several countries, in light of its low costs and some degree of effectiveness. The demonstration of specific neurochemical changes, induced by STN-DBS, as this review will demonstrate, should contribute to swing the *pendulum* further in favour of DBS. Yet, so far, blindly rated assessment of lesion- and DBS-mediated effects are not available, to our knowledge.

As a matter of fact, pallidotomy or subthalamotomy (Gross et al., 1997; Jourdain et al., 2014; Lang et al., 1999; Lozano et al., 1998) and stereotactic thermolytic lesions were common therapy in the 60's before the introduction of levodopa (LD) (Svennilson et al., 1960). After a prolonged decline, since the early 90's, stereotactic neurosurgery has regained a central role in treating movement disorders despite the success of pharmacological therapies. For the purpose of this review, it is important to acknowledge how extensively DBS, and particularly STN-DBS, has been changing our pharmacological regimen, allowing for the minimization of drug-induced side effects or inappropriate LD loading (Alexoudi et al., 2015; Antonini et al., 2013; Shalash et al., 2014; Zibetti et al., 2009).

The development, from pioneering discoveries to modern techniques, is fascinating. Pre-LD surgical attempts were based on the paradoxical strategy of adding a lesion to an already impaired brain circuitry. However, modern ideas arose from the clinical experience itself, when the unintended ligation of the anterior choroidal artery in a patient suffering from PD lead to the cessation of rest tremor (Cooper, 1956). In the following years, Leksell improved the method by introducing his stereotaxic frame (Leksell et al., 1987) and by using thermo-coagulation in order to accurately target the internal globus pallidus (GPi; Svennilson et al., 1960). Nevertheless, little was known about the biochemical mechanism (if any) behind the clinical efficacy of a lesion placed at this site on the dysfunctional circuitry underlying PD and other movement disorders.

However, during the long lasting undisputed supremacy of LD, the synergistic interplay between clinical disease and animal models was revitalized, by the chance discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in human (Langston et al., 1983). The primate MPTP-model of PD served to demonstrate that the STN lesion reversed the motor symptoms as predicted by the classical BG scheme (Bergman et al., 1994, 1994; Langston et al., 1984; Wichmann et al., 2011). In a recent editorial, Benazzouz et al. (2015) refer to the interplay between mammalian disease models and effective therapies in humans, leading to human STN-DBS (see also Galati and Stefani, 2015). Although STN-DBS represents the mainstream approach, other targets have also proved to be effective. Pallidal stimulation has beneficial effects in PD patients (Follett et al., 2010; Stefani et al., 1999), reproducing those resulting from pallidal lesioning (Siegfried and Lippitz, 1994). In addition, different groups have been exploring the benefits provided by structures beyond the