Deep brain stimulation and chemical neuromodulation: current use and perspectives for the future

C. Hamani, J. S. Neimat, and A. M. Lozano

Division of Neurosurgery, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

Summary

During the last decade there has been a marked increase in the applications of deep brain stimulation for the treatment of neurological and psychiatric disorders. In addition, the last years were marked by the first studies using the intraparenchymal administration of drugs into the brain. There have been improvements in outcome and an increase in the number of surgical candidates and conditions to be treated. This will act as a driving force to improve the technology applied to design and manufacture new devices.

Keywords: Deep brain stimulation; movement disorders; pain; epilepsy; Tourette’s syndrome; obsessive-compulsive disorder; depression; vagus nerve stimulation.

Introduction

In the last decade deep brain stimulation (DBS) has become established as an accepted and important therapy in the field of Functional Neurosurgery. The knowledge gained with the application of DBS for movement disorders and pain has already been leveraged towards the treatment of other disorders, including epilepsy and psychiatric conditions. In addition to stimulation, the last years were marked by the first trials using the intraparenchymal administration of drugs, namely glial cell line-derived neurotrophic factor (GDNF) for the treatment of Parkinson’s disease (PD) [22].

In the years to come, we expect to see a considerable expansion of the indications for DBS and the establishment of new techniques of chemical neuromodulation. This review will focus on the areas of current and future engagement and investigation in these rapidly growing fields.

Deep brain stimulation

Movement disorders

The treatment of movement disorders has been revolutionized by the therapy of deep brain stimulation (DBS). The ability to reversibly and adjustably inhibit selected targets has enabled bilateral treatment and obviated the need for tissue destruction. It has thus seen a far increased application in disease treatment.

Parkinson’s disease

Most centers to date are currently favoring the use of subthalamic nucleus (STN) DBS over other targets for the treatment of Parkinson’s disease (PD) [23]. Studies using double blind assessment have demonstrated that bilateral STN stimulation provides lasting improvements in tremor, rigidity, the involuntary movements induced by levodopa, and to a lesser extent bradykinesia, gait and postural instability [34].

To be considered a good candidate for STN DBS, patients have to be diagnosed with PD, present disabling motor fluctuations, a prolonged “off” state, significant dyskinesias, and a good clinical response to levodopa [14, 27, 58, 66, 68, 83]. The last item is particularly important as the response to levodopa seems to predict clinical outcome [12]. The main exclusion criteria for STN DBS in most centers are the presence of significant cognitive and psychiatric symptoms, medical problems that might pose a risk for the patient during the procedure (i.e. coagulopathies), a poor response to levodopa, and old age (more than 70 years) [14, 27, 58, 66, 68, 78, 83].
To overcome some of these problems, the use of different surgical targets has been advocated. Motor cortex stimulation (MCS) is being examined as an alternative for patients at high risk for DBS [10]. Even though results with this technique are still preliminary, the clinical benefit does not seem to match that achieved with STN DBS. Anecdotal reports have shown that stimulation of the pedunculopontine nucleus (PPN) can be safely performed in surgical candidates [49]. As PPN DBS ameliorates akinesia in non-human parkinsonian primates [30] and is involved in mechanisms of gait [56], results from this preliminary trial are much awaited. Despite of these few innovative approaches, it is worth mentioning that most non-dopaminergic parkinsonian symptoms, including speech problems, cognitive and psychological difficulties, bladder, bowel and sexual dysfunction, among others, as they are resistant to both levodopa and surgery and still pose a major disability to patients with advanced PD. This should be taken into account in the development of future alternative therapies to treat patients with PD.

Another major challenge in the future will be to devise therapies that not only treat the symptomatology of PD but that are also capable of arresting the progression of the illness. While it has been hypothesized that early surgical interventions could reduce nigral degeneration due to a decrease in glutamatergic release by the STN [61], this has not been clearly demonstrated so far. In the clinical scenario, one of the trials addressing this issue is using gene therapy with the premise that one could reduce STN glutamatergic overdrive by altering the phenotype of its cells into GABAergic neurons [16]. This phase I clinical trial has been designed mainly to assess the safety of the procedure and the escalation of doses of the viral injections [32]. Yet, as a similar approach was protective in animal models of PD [46], the outcome of this series of patients is highly awaited.

There has been much interest on the administration of GDNF to treat PD. In parkinsonian non-human primates and rodents, studies have shown that the intraventricular or intraparenchymal administration of GDNF was neuroprotective and able to induce regeneration of tyrosine hydroxylase-positive terminals in the substantia nigra and striatum [3, 69]. As a result, clinical trials have been set and initially attempted the intraventricular administration of the drug with no significant improvement [52]. It has been hypothesized that the relative size of the human brain made the transependymal diffusion of GDNF insufficient to create the necessary concentrations of the drug to produce an effect. Clinical trials were then designed to deliver GDNF directly into the brain parenchyma. Gill et al. demonstrated a 39% improvement in Unified Parkinson’s Disease Rating Scale (UPDRS) motor scores at 1 year and no significant adverse effects with the intraputaminal administration of the drug [22]. In addition, they observed a significant increase in striatal dopamine levels as assessed by positron emission tomography (PET) [22]. These promising results were the basis for a phase II multicenter study with a randomized blinded crossover design. Unfortunately, this study showed no significant differences in UPDRS motor scores between patients that received GDNF or placebo at 6 months (Amgen press release June 28, 2004). The reasons for the discrepancies between the open label and the blinded trials are still unclear but may be due to the dose of medication injected, the tip diameter of the catheters, issues related to the delivery/diffusion of the GDNF, or a placebo effect in the open label study. Animal studies with other neurotrophins are under way but new clinical studies using these agents are likely not to occur so soon.

Dystonia and tremor disorders

Bilateral globus pallidus internus (GPi) stimulation has become an important therapeutic alternative for the treatment of dystonia [7, 15, 35, 38, 45, 77]. The clinical response to surgery seems to be dependent on etiology, with primary generalized and cervical dystonia responding better than secondary dystonia [18, 37, 44, 76]. In addition, patients with the DYT1 mutation seem to be good candidates for pallidal DBS, with reports demonstrating a 50–80% decrease in Burke-Fahn-Marsden severity scores (BFMDS) 12 months after the procedure [13, 15, 18, 35]. Improvement in patients with non-DYT1 primary generalized dystonia is on the order of 40–60% [15, 18, 35, 36]. Patients with secondary dystonia have an overall reduction of 10–35% in BFM scores after GPi DBS [18, 35].

The improvement in cervical dystonia as assessed by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is in the order of 60–80% [19, 35, 37]. It has been noted by several authors that the time course of response for pain is quicker than for motor symptoms and disability. Long-term follow-up studies are still needed to assess whether the improvements observed with surgery are long lasting.

In addition to the GPi, stimulation of the subthalamic nucleus is currently being explored for the treatment of generalized dystonias with anecdotal reports showing promising results [67].