Neuromodulation for neurodegenerative conditions

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1. ABSTRACT

Pharmacological therapy has had limited success in the treatment of most major neurological diseases. This has motivated the development of a number of novel surgical approaches designed to ameliorate drug-induced side effects or pharmacoresistant symptoms. Deep brain stimulation (DBS) has been quite successful in controlling both the cardinal motor manifestation of Parkinson’s disease and the side effects of prolonged levodopa therapy. This has encouraged the application of DBS technology to treat a number of other neurodegenerative conditions, including secondary dystonia associated with pantothenate kinase-associated neurodegeneration (PKAN, formerly Hallervorden–Spatz syndrome), chorea associated with Huntington’s disease, and most recently, cognitive decline associated with Alzheimer’s type dementia. We review the rationale, indications and outcomes of neuromodulation for selected neurodegenerative conditions. In addition to DBS, we discuss select small molecule and gene-based neuromodulatory approaches. Ongoing study of basic pathophysiological mechanisms may eventually allow directed primary prevention of some of these diseases, but until then, invasive neuromodulation will likely continue to play an ever-increasing role in the delivery of the most advanced care for patients with these debilitating conditions.

2. INTRODUCTION

No cure has yet been found for any major neurodegenerative disease. Nonetheless a number of pharmacological regimens have been developed to relieve symptoms and decrease the burden of disease associated with many forms of neurodegeneration. Perhaps the most celebrated historical example was the development of levodopa therapy for Parkinson’s disease (1, 2), but recognition of severe drug induced side-effects dampened initial hopes (3). The search for ever more effective pharmacological targets continues to dominate research into novel therapies for most neurodegenerative disorders. Still a clinically effective neuroprotective agent remains elusive, and progress in finding better pharmacological therapy for most major neurodegenerative disease has been slow. Drug-induced side effects and pharmacoresistant symptoms have driven attempts to treat a number of neurodegenerative diseases using invasive neurosurgical techniques. Here we review some standard surgical options used to treat Parkinson’s disease and emerging applications to other forms of neurodegeneration, like pantothenate kinase-associated neurodegeneration (PKAN) and Huntington’s disease. We also review a novel application of deep brain stimulation (DBS) designed to slow cognitive decline associated with Alzheimer’s disease. A number of advances have been made in the area of cell and gene therapy for neurodegenerative disease, many of which
employ surgical delivery methods. Several excellent reviews of these topics have recently been published elsewhere (4-6), but we will highlight some particularly interesting gene-based neuromodulatory approaches, including optogenetics, and comment on their potential clinical utility.

The field of neuromodulation is currently among most innovative areas in biomedicine. A number of remarkable discoveries have been made serendipitously through keen clinical observation and, more recently, by rational application of basic discoveries brought to the bedside. In this brief review we focus on established and emerging technology that has been used to treat a variety of conditions associated with some of the most devastating neurodegenerative diseases. Neuromodulation may be defined as the use of a therapeutic device to change the physiological function of the nervous system without grossly disrupting its anatomical integrity. Most forms of neuromodulation discussed in this review are closely associated with the field of functional neurosurgery and have in many cases been pioneered by neurosurgeons themselves. Today deep brain stimulation is perhaps the dominant expression of modern neuromodulation, owing principally to its perceived safety, reversibility and adaptability. Standard stimulating electrodes can be reliably placed virtually anywhere in the neuroaxis and stimulation parameters can later be exquisitely tailored by adjusting current or voltage, pulse widths and frequency to titrate optimal therapy while avoiding off-target adverse effects. The success of DBS in treating a wide variety of conditions has to some extent overshadowed other, no less innovative approaches. These include a number of emerging surgical applications designed to deliver small molecules, genes and even cells to repair the dysfunctional central nervous system. We discuss a few other selected applications of innovative technology in the context of neurodegenerative disease, including viral vector delivery of neuromodulatory genes and intraventricular delivery of baclofen. These approaches remain investigational but have shown significant promise in preliminary studies. We will not discuss other approaches to neuromodulation, like transcranial magnetic or direct cortical stimulation, motor cortex stimulation, dorsal column implants, or low energy focused ultrasound. Although these approaches offer the possibility of a less invasive form of neuromodulation, their efficacy in treating the manifestations of neurodegeneration in humans has not yet been clearly established.

3. NEUROMODULATION FOR NEURODEGENERATIVE DISEASE

3.1. Cardinal and drug-induced symptoms in Parkinson’s disease

Current clinical interest in deep brain stimulation (DBS) gained significant momentum as drug-induced motor side effects of prolonged levodopa therapy become widely recognized. To date, more than 80,000 patients have been treated with DBS. The ideal surgical candidate with Parkinson’s disease has no evidence of cognitive decline, has maintained a clear response to levodopa, and suffers motor fluctuations and dyskinesia despite an optimal oral regimen. The cardinal motor symptoms of Parkinson’s disease, tremor, rigidity and bradykinesia, respond well to DBS, but the most common current indication for surgical intervention in Parkinson’s disease is the dose-limiting side effects of chronic levodopa therapy, motor fluctuations and dyskinesia (7-9). A number of large clinical trials established the safety and efficacy of pallidal and subthalamic stimulation for Parkinson’s disease (10-12), and recent studies suggest that DBS may be cost effective despite the high initial expense (13-15). Implantation of chronic stimulating electrodes into the subthalamic nucleus (STN) or internal segment of the globus pallidus (GPi) was approved by the US Food and Drug Administration (FDA) in January 2002 and is now a widely recognized standard of care for patients with advanced disease (16). More recently there has been increasing interest in implanting patients earlier in the natural history of the disease in the hope of delaying or avoiding levodopa-induced sided effects (17, 18). These ongoing studies should provide objective data to better guide practitioners on optimal timing for DBS surgery. Detailed mechanisms of DBS remain elusive, but high-frequency stimulation of either target is thought to disrupt pathological oscillatory activity within the basal ganglia and prevent its transmission throughout the neuroaxis (19, 20). Several studies have found that reduction in preoperative levodopa is possible following STN stimulation but that similar reductions in medication cannot be achieved after pallidal stimulation owing to resistant bradykinesia (21-24). On the other hand, a few studies suggest that reduction in levodopa daily equilibrium following STN stimulation may be associated with cognitive decline that is sometimes seen following surgery at this target (25-27). Some medication-resistant symptoms including gait and postural disturbances respond only transiently or more variably to STN and GPi DBS surgery (28, 29). Other medically-refractory symptoms, including speech dysfunction (30, 31), cognitive impairment (32, 33) and some psychiatric manifestations (34, 35), may be aggravated by DBS, making a thorough pre-operative neuropsychological assessment of each patient mandatory.

Increasing recognition of debilitating non-motor parkinsonian symptoms has prompted a search for novel surgical interventions (36). Disorders of cognition, mood, gait and posture, sleep, olfaction, and autonomic regulation are levodopa non-responsive symptoms of Parkinson’s disease and are major drivers of disability and decreased quality of life in this population (37, 38). With disease progression, nearly all patients with Parkinson’s disease will develop these impairments despite optimal medical and surgical care (39). For example, long-term longitudinal studies show that the incidence of Lewy body dementia is 50 percent at 10 years and 83 percent at 20 years. Ten years after the diagnosis of Parkinson’s disease, more than 50 percent of patients with Parkinson’s disease experience frequent falls. At 20 years, many of these patients have suffered a fracture as a consequence of their falls (40). Recognition that gait impairment and postural instability underlie significant mortality and morbidity has generated renewed interest in understanding the pathophysiology of gait (41), and motivated the investigation of a novel target.
for DBS in the area of the pontomesencephalic junction to treat parkinsonian postural instability. The anatomical location of midbrain locomotor regions were first identified in early work on decerebrate cats (42). In bipedal animals these areas are thought to correspond to the region of the pedunculopontine nucleus complex (43). A number of groups have implanted standard DBS electrodes into the pedunculopontine nucleus to study the effect of low frequency stimulation on postural stability (44-47). Moro et al. (48) document sustained reduction in falls and freezing in six patients with advanced Parkinson’s disease who received a unilateral pedunculopontine stimulator. Similarly, Theyavasan et al. found in a reduction in postural instability and falls in a prospective series of five patients who received bilateral stimulation to the mid-lower PPN (49). Other studies (50, 51) suggest that co-stimulation of other nuclei within the basal ganglia in conjunction with the PPN may provide a greater clinical benefit. Approximately 100 patients worldwide have now undergone similar therapy. Long-term controlled trials will be required to address a number of outstanding issues including the precise target of electrical stimulation within the pedunculopontine region, selection of best responders, and durability of the intervention.

Additionally, several early human studies involving neuromodulation by gene manipulation for the treatment of Parkinson’s disease are underway (52, 53). One emerging approach is the direct infusion of an adeno-associated viral vector (AAV) carrying a cassette to induce the expression of glutamic acid decarboxylase (GAD), the catalytic enzyme in the synthesis of GABA, within excitatory glutaminergic neurons of the STN (54, 55). This interesting approach ostensibly addresses STN overexcitability, caused by pathologically decreased dopaminergic input to the indirect pathway, and decreases inhibitory output by neurons in the internal segment of the globus pallidus and pars reticulata. Although questions remain regarding the durability of this treatment, a recent trial demonstrated that patients who received AAV2-GAD injections in the STN showed potential improvement in motor-related Parkinson’s symptoms when compared to a sham surgery control group (55). Additionally, there are several ongoing studies which use adeno-associated viral vectors for delivery of various other gene products to different sites within the basal ganglia. One such study aims to alter functional connections by increasing dopamine production within the striatum (56), and another hopes to protect against degeneration of dopaminergic neurons with growth factors (57, 58). The efficacy of these approaches will be defined by the results of ongoing trials.

3.2. Dystonia in PKAN

Based on the success of pallidal stimulation to treat dystonia that occurs sporadically in a subset of patients with Parkinson’s disease and in patients with primary dystonia (59-64), high-frequency GPi DBS has recently been attempted to treat other neurodegenerative disease where dystonia develops secondary to basal ganglia degeneration. Interestingly, the effect on dystonia is not instantaneous as with tremor capture in Parkinson’s disease, but requires several weeks of continuous stimulation to achieve an optimal antidystonic effect. This suggests a different mechanism of action. Among other mechanisms, stimulation induced plasticity mediated by trophic factor upregulation has recently been investigated in animal models (65, 66). Pallidal stimulation for primary dystonia was FDA approved under a humanitarian device exemption in 2003, and has been applied off label for the treatment of secondary dystonia associated with certain neurodegenerative diseases. Among the most responsive is dystonia associated with pantothenate kinase-associated neurodegeneration (PKAN), a form of neurodegeneration with brain iron accumulation formerly called Hallervorden-Spatz syndrome (67, 68). In several single case studies and a small case series reporting one year follow-up data, motor improvements ranged between 46 percent and 92 percent (69-73). These outcomes are actually somewhat better than those documented in high-level controlled trials of bilateral GPi DBS for primary dystonia, and may indicate a positive publication bias (74). Indeed, a recent large retrospective study that captured all cases of dystonia secondary to brain iron accumulation treated worldwide showed that bilateral pallidal stimulation revealed less dramatic but still overall positive motor improvements in 14 patients with PKAN (75). As with Parkinson’s disease, no study has provided any evidence of underlying disease modification following GPi stimulation in patients with this disease. All patients with PKAN eventually develop characteristic anatomical abnormalities in the basal ganglia from progressive iron accumulation in the globus pallidus. In cases with the longest follow-up, a steadily decline in stimulation efficacy occurs over several years after implantation (69).

Another interesting form of neuromodulation for dystonia involves the use of intrathecal baclofen (ITB) delivered to the spinal column. This therapy, developed several years before the advent of pallidal stimulation, was initially conceived to avoid cognitive dysfunction associated with oral baclofen therapy (76, 77). It has recently been used to treat rigidity and spasticity associated with various forms of secondary dystonia including PKAN (78-82). This form of chemical neuromodulation acts centrally to reduce motor hyperactivity within the descending corticospinal tract at the level of spinal interneurons. No head-to-head trials have established its efficacy compared with pallidal stimulation, and several studies have found that ITB is associated with an anticipated rate of scoliosis in children (83-86). The effectiveness of this therapy on arm and neck dystonia has been debated (78, 87) and has led to a recent attempt to administer baclofen intraventricularly using catheters introduced stereotactically into the third ventricle. Promising efficacy and safety data have recently been published by Albright et al. (88, 89) where its effect on dystonia associated with advanced PKAN suggests outcomes on par with and perhaps superior to DBS. We await blinded controlled studies to validate this emerging form of chemical neuromodulation.

3.3. Chorea in Huntington’s disease

Earlier studies demonstrated the potential effectiveness of lesions in the globus pallidus for control of chorea (90, 91), and recently some centers have begun to re-explore the possibility of surgically palliating intractable
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hyperkinetic movement associated with Huntington’s disease using chronic pallidal stimulation. Only six cases have so far been reported. While outcomes of GPI DBS for Huntington’s chorea have been variable, all reported significant reductions in the chorea (39–77 percent) following bilateral insertion of electrodes into the posteroventral pallidum with no apparent effects on cognitive decline (92–96). Most, but not all (94), studies showed that higher frequency stimulation (130-180 Hz) is more effective than low frequency stimulation (40 Hz) for controlling chorea. However, high frequency stimulation worsened bradykinesia in some cases (92–94). Given the small number of studies, positive selection bias is again possible and larger case series are needed to clarify optimal patient selection criteria, the most effective stimulation parameters, and durability of the intervention.

3.4. Cognition in Alzheimer’s type dementia

Alzheimer’s disease is the most common form of adult-onset dementia. Globally about 27 million people are affected, and its prevalence is predicted to increase significantly as world population ages (97). The disease is characterized by impairment in the neural circuits serving cognitive and memory functions, particularly in the hippocampal/entorhinal cortical complex where the neurodegenerative burden of the disease is highest. The nucleus basalis of Meynert (NBM), which has wide projections to the neocortex, was explored as an early target for neuromodulation in Alzheimer’s dementia by Turnbull et al. in 1985. This case report demonstrated that, while unilateral electrode stimulation of the NBM did not result in clinical improvement of dementia, increased cortical glucose metabolic activity was seen in the ipsilateral temporal and parietal lobes (98). More recently, bilateral stimulation of the NBM has shown some improvement in cognitive function in patients with Parkinsonian dementia (99).

Another approach, fornical stimulation, was based on a serendipitous clinical observation during an attempt to stimulate the lateral hypothalamus for obesity (100, 101). The Toronto group hypothesized that electrical stimulation of the fornix, part of the Papez memory circuit (102, 103), might be used to improve working memory and cognitive function in patients with Alzheimer’s-type dementia. Six patients with advanced disease were recruited for a phase I safety trial (104) where deep brain stimulators were placed bilaterally along the anteromedial border of the fornix bundle. After one year of high-frequency fornical stimulation, glucose hypometabolic uptake within the temporoparietal cortex was largely reversed. Behavioral testing suggested that the rate of cognitive decline for patients in this study may have been delayed. All patients remained on acetylcholinesterase inhibitors. This pilot study demonstrates the safety and potential efficacy of deep brain stimulation to treat the cognitive decline that accompanies Alzheimer’s disease and has motivated a large multi-center clinical trial to fully assess the therapeutic effect of this intervention.

3.5. Optogenetics: the future of neuromodulation?

It is now possible to use light, rather than electrical stimulation, to modulate the activity of neural circuits. In theory, optogenetic stimulation may be an improved method for modulating discrete neural targets by avoiding off-target adverse effects often encountered with spread of electric charge around a DBS electrode. The selectivity of an optogenetic approach lies in the specificity of viral vectors designed to target specific cell types (105-108). These viral vectors infect the cell with light-sensitive plasma membrane channels capable of permitting rapid entry of sodium and other cations (via the channelrhodopsin pore) or chloride (via the halorhodopsin transporter) with concomitant excitation or inhibition of the neuron (109). Only those neural elements expressing the light-sensitive protein are stimulated. This method may provide greater specificity and reduce the collateral side effects compared with standard electrical stimulation (110). There are many practical and regulatory obstacles to using this technique clinically, but the theoretical advantages of optogenetic stimulation might make this effort worthwhile.

4. SUMMARY AND PERSPECTIVE

New applications of neuromodulation initially developed to treat motor disability associated with Parkinson’s disease are currently being adapted to treat a number of symptoms associated with other neurodegenerative conditions, including PKAN, Huntington’s disease and Alzheimer’s type dementia. Deep brain stimulation may be able to provide symptomatic relief of dystonia, chorea and cognitive decline associated with these conditions, but it has not been shown that this form of neuromodulation can retard ongoing neurodegeneration in humans. There are, however, tantalizing clues from recent studies in rodents that clearly demonstrate enhanced neurogenesis following high frequency stimulation of afferent input to the denate gyrus (66, 111, 112). If similar DBS-induced neurogenesis occurs in other systems and in humans, it may be possible to harness the brain’s own regenerative capacity to find a path to true neurorestoration. Many other forms of neuromodulation have been attempted in humans. So far, the most successful have been direct delivery of central baclofen and, more recently, AAV delivery of various genes to the basal ganglia. It is not yet clear that any alternative form of neuromodulation, established or experimental, offers a superior safety and efficacy profile compared with deep brain stimulation for any neurodegenerative condition.

5. ACKNOWLEDGMENTS

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