REVIEW ARTICLE

Deep brain stimulation: potential for neuroprotection

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Abstract

Over the last two decades there has been an exponential rise in the number of patients receiving deep brain stimulation (DBS) to manage debilitating neurological symptoms in conditions such as Parkinson's disease, essential tremor, and dystonia. Novel applications of DBS continue to emerge including treatment of various psychiatric conditions (e.g. obsessive-compulsive disorder, major depression) and cognitive disorders such as Alzheimer's disease. Despite widening therapeutic applications, our understanding of the mechanisms underlying DBS remains limited. In addition to modulation of local and network-wide neuronal activity, growing evidence suggests that DBS may also have important neuroprotective effects in the brain by limiting synaptic dysfunction and neuronal loss in neurodegenerative disorders. In this review, we consider evidence from preclinical and clinical studies of DBS in Parkinson's disease, Alzheimer's disease, and epilepsy that suggest chronic stimulation has the potential to mitigate neuronal loss and disease progression.

Introduction

Deep brain stimulation (DBS) involves the implantation of electrodes into targeted regions of the brain for chronic delivery of electrical stimulation from an implantable pulse generator. Continuous high-frequency stimulation of subcortical structures such as the subthalamic nucleus (STN) and globus pallidus pars interna (GPi) has become a well-established treatment of motor symptoms in patients with Parkinson's disease (PD).[1] Encouraged by this success, researchers have since found new neuroanatomical targets of DBS to treat other motor disorders (e.g. freezing of gait, tardive dyskinesia, secondary dystonia), epilepsy, psychiatric conditions (e.g. obsessive-compulsive disorder, major depression) and more recently, Alzheimer's disease.[2]

Despite more patients receiving DBS surgery, the mechanisms underlying its therapeutic effect remain unclear. At the site of electrode implantation, DBS may modulate local neuronal activity by direct stimulation of axons and dendrites.[3] Alterations in local firing patterns could also have important effects on the synchronization of neuronal networks by disrupting pathological oscillatory activity in diseased brain regions (e.g. excessive β oscillations in the basal ganglia of PD patients).[3] This electrical modulation relieves motor symptoms within seconds of current onset, as shown by the immediate relief of essential tremor when current is delivered through a DBS electrode in the ventral intermediate nucleus of the thalamus (VIM).[4] However, growing evidence suggests that DBS is more than just a "neuromodulatory switch" to control debilitating motor symptoms. Chronic DBS has been shown to induce gradual reorganization of neuronal circuits through enhanced synaptic plasticity and neurogenesis.[4] In addition, recent studies in preclinical animal models and humans suggest that DBS may also protect neurons from disease-related neurotoxicity in certain conditions. This raises the exciting possibility that DBS may have the unanticipated benefit of

slowing rates of disease progression or even improving long-term survival in some patients.

Here, we review evidence from preclinical and clinical studies of DBS in Parkinson's disease, Alzheimer's disease, and refractory epilepsy to determine whether chronic neuromodulation could have neuroprotective properties with clinical relevance. We have limited our review to these disorders, since they are all characterized by a progressive neurodegenerative phenotype culminating in neuronal loss. For a treatment to be considered "neuroprotective" or "disease modifying," it will be important to demonstrate that it: (1) has an effect on disease pathogenesis; (2) reduces the rate of neuronal loss and (3) is associated with slower symptom progression or an improvement in survival.

Methods

The authors searched the online PubMed database for peer-reviewed articles published in English between 1 January 1987 and 1 May 2018. The search term "deep brain stimulation" combined with either "Parkinson's disease," "Alzheimer's disease," or "epilepsy" was used. Articles for in-depth review were next identified by the authors by searching the article title, abstract, and keywords for mention of "neuroprotection," "neuroprotective," "disease modifying," "survival," "neuronal loss," "apoptosis," "synaptic dysfunction," "synaptic loss," or "neurotoxicity." Additional articles were identified by screening reference lists of recent review articles focusing on mechanisms of DBS.

Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting an estimated 2–3% of adults over the age of 65 years.[5] It is characterized by intracellular accumulation of misfolded forms of α-synuclein and progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc).[5] Evidence from clinical-pathological correlation studies suggests that early depletion of these dopaminergic neurons is the likely cause of characteristic motor features, such as bradykinesia & rigidity.[5] Neuronal loss has also been reported in various other brain regions including the locus ceruleus, nucleus basalis of Meynert, raphe nucleus, pedunculopontine nucleus, dorsal motor nucleus of the vagus, amygdala, and hypothalamus.[5] In the absence of disease-modifying therapies, current treatment is primarily focused on controlling motor symptoms using drugs that enhance intracerebral dopamine concentrations (e.g. levodopa, selegiline) or stimulate dopamine receptors (e.g. pramipexole). In the long-term, complications of dopaminergic treatment, including on/off motor fluctuations and dyskinesias, frequently occur.[5] DBS of subcortical structures such as the STN, GPi, and occasionally VIM, may be offered as an established treatment for well-selected patients with levodopa-responsive motor symptoms who experience disabling medication-related side effects.[6] The mechanism underlying DBS-mediated motor symptom control remains uncertain, however it is likely to involve both local effects on neuronal firing patterns and network-wide effects on pathological oscillatory activity.[3,7] In addition to effective relief of motor symptoms, emerging evidence from preclinical models suggests that long-term DBS may have the potential to protect against neuronal loss and limit motor dysfunction. However it remains uncertain whether this occurs by mitigating pathological oscillatory activity or through other mechanisms.

Neuroprotection in PD animal models

Early evidence that DBS could have neuroprotective properties arose from studies of STN-DBS in preclinical models of PD. Chronic STN stimulation in rats was shown to protect dopaminergic neurons in the SNpc from the toxic effects of intrastriatal 6-hydroxydopamine (6-OHDA) administered 5–7 days previously.[8,9] To exclude an effect on uptake or metabolism of 6-OHDA, a later study by Spieles-Engemann et al. delayed STN-DBS to 2 weeks after 6-OHDA administration, once significant neuronal loss had already occurred.[10] Rats treated with STN-DBS again showed increased survival of dopaminergic neurons in the SNpc suggesting a *bona fide* neuroprotective effect. In another study, stimulation of the rodent analogue of the GPi, the entopeduncular nucleus, did neither mitigate 6-OHDA-mediated behavioral deficits nor loss of dopaminergic neurons, suggesting neuroprotective effects could be restricted to certain stimulation targets.[11] Alongside rodent models, DBS has also been shown to protect against neurotoxicity in nonhuman primate models of PD. Following 1-methyl-4-phenyl-1, 2, 3, 6- tetrahydropyridine (MPTP) administration in monkeys, STN-DBS was shown to limit dopaminergic neuronal loss in the SNpc[12,13] and periaqueductal grey matter (PAG).[13] Interestingly, less neuronal rescue was observed in animals with more severe MPTP lesions,[12] suggesting that DBS may only protect neurons from milder forms of neurotoxicity and that there may be a threshold of severity of dopaminergic neuronal loss after which neuronal rescue and associated behavioral rescue may no longer be possible.

Despite being widely used in preclinical research, toxin models of PD have limited translational value due to the acute nature of MPTP or 6-OHDA lesions and the absence of key neuropathological features, most notably

α-synuclein aggregates.[14] To mirror the clinical phenotype more closely, two recent studies have examined the effect of STN-DBS in non-toxicant-based PD animal models. Mussachio et al. studied the effect of chronic STN-DBS in rats with viral vector-mediated nigrostriatal overexpression of human A53T α-synuclein.[15] As in PD patients, these animals develop a progressive neurodegenerative phenotype with accumulation of insoluble α-synuclein aggregates, dopaminergic neuronal loss in the SNpc and motor impairment.[16] To mimic a moderate stage of human PD, chronic STN-DBS was commenced 3 weeks after mutant α-synuclein expression, at which point striatal dopaminergic fiber loss and motor deficits were already established. High frequency STN stimulation reversed motor deficits and was accompanied by higher numbers of tyrosine-hydroxylase-(TH) expressing SNpc neurons compared with unstimulated rats.[15] Motor improvements were sustained 24 h after stimulation was terminated, suggesting a disease-modifying effect of STN-DBS.[15] Despite rescue of TH-positive SNpc neurons and improved motor function, striatal dopamine levels remained depleted in rats treated with chronic STN stimulation.[15] This suggests that dopaminergic terminals in the striatum may be particularly vulnerable to A53T α-synuclein-mediated toxicity, resulting in early synaptic loss before the onset of DBS treatment.

A later study by Fischer and colleagues studied the effect of chronic STN-DBS in a different PD rat model characterized by viral vector-mediated nigrostriatal over-expression of human *wild-type* α-synuclein.[17] Despite low levels of transgene expression and a relatively mild clinical phenotype, STN-DBS did not protect against forelimb akinesia, striatal denervation, or SNpc neuronal loss. These findings are in contrast to those of Mussachio et al., which could partly be explained by differences in mechanisms of neurotoxicity arising from mutant and wild-type alpha-synuclein,[18] as well as variation in stimulation currents used. This highlights the need for further research to evaluate the reproducibility of the above findings across different preclinical PD models, including transgenic α-synuclein mice and viral vector-based rodent and nonhuman primate α-synuclein expression models. In addition, it will be important to evaluate the effect of different stimulation parameters (i.e. frequency, pulse width, current, voltage, and duration) on the neuroprotective potential of STN-DBS.

The mechanisms by which DBS may mitigate the loss of dopaminergic neurons are not well understood. Several studies have proposed that STN-DBS may protect SNpc neurons by reducing excitotoxicity arising from overactive glutamatergic projections which originate in the STN.[12,19,20] This hypothesis is based on the observation that STN-DBS has very similar effects to STN lesions in toxin models of PD.[12,21–23] Experimental data supporting this proposed neuroprotective mechanism are currently lacking. Indeed there is electrophysiological evidence that white matter tracts surrounding the STN may also be simultaneously stimulated by DBS thus making it difficult to parse out if the observed effect is only due to reduced glutamatergic outflow from the STN.[3] In addition to limiting excitotoxicity, STN-DBS may promote neuronal survival by stimulating the release of neurotrophic factors. STN-DBS has been shown to increase levels of brain-derived neurotrophic factor (BDNF) in the nigrostriatal system and primary motor cortex of 6-OHDA lesioned rats.[10,24] Following release, BDNF binds the transmembrane receptor tropomyosin-related kinase type B (trkB) resulting in activation of three intracellular signalling cascades: (1) mitogen-activated protein kinase/extracellular signal related-kinase (MAPK/ERK) which promotes protein synthesis; (2) phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) which regulates protein translation/trafficking and inhibits apoptosis; (3) phospholipase Cγ/protein kinase C (PLCγ/PKC) which is involved in the regulation of synaptic plasticity.[25] Using the 6-OHDA rat model, Fischer et al. recently demonstrated that chronic STN-DBS results in phosphorylation of Akt and ribosomal protein S6 in SNpc neurons, suggesting activation of the BDNF/trkB signalling pathway.[26] In addition, STN-DBS-mediated rescue of SNpc neurons was abrogated by selective pharmacological blockade of the trkB receptor.[26] Taken together, these findings identify BDNF/trkB signalling as a possible mechanism for STN-DBS-mediated neuroprotection (Fig. 1). Since activity-dependent BDNF release is believed to occur at dendrites,[27] STN-DBS may have greater protective effects if initiated at an early stage of disease when synaptic degeneration is less advanced.

Does DBS modify disease progression in patients?

Despite promising reports of DBS-mediated neuroprotection in PD animal models, there is limited evidence from clinical studies to support a similar disease-modifying effect in patients. Follow-up studies of STN-DBS patients over a 3–10 year period have revealed sustained symptomatic benefit in terms of levodopa-responsive motor symptoms (e.g. tremor, rigidity) and dyskinesias.[28] Most longitudinal cohort studies have reported stabilization or a trend towards improvement in off-medication/off-stimulation motor scores compared with preoperative baseline.[28] Despite evidence of slowed progression of motor deficits, a recent ^{18}F-fluorodopa positron emission tomography (PET) study reported continuous decline in dopaminergic function in patients with advanced PD despite STN-DBS.[29] Furthermore, a postmortem analysis
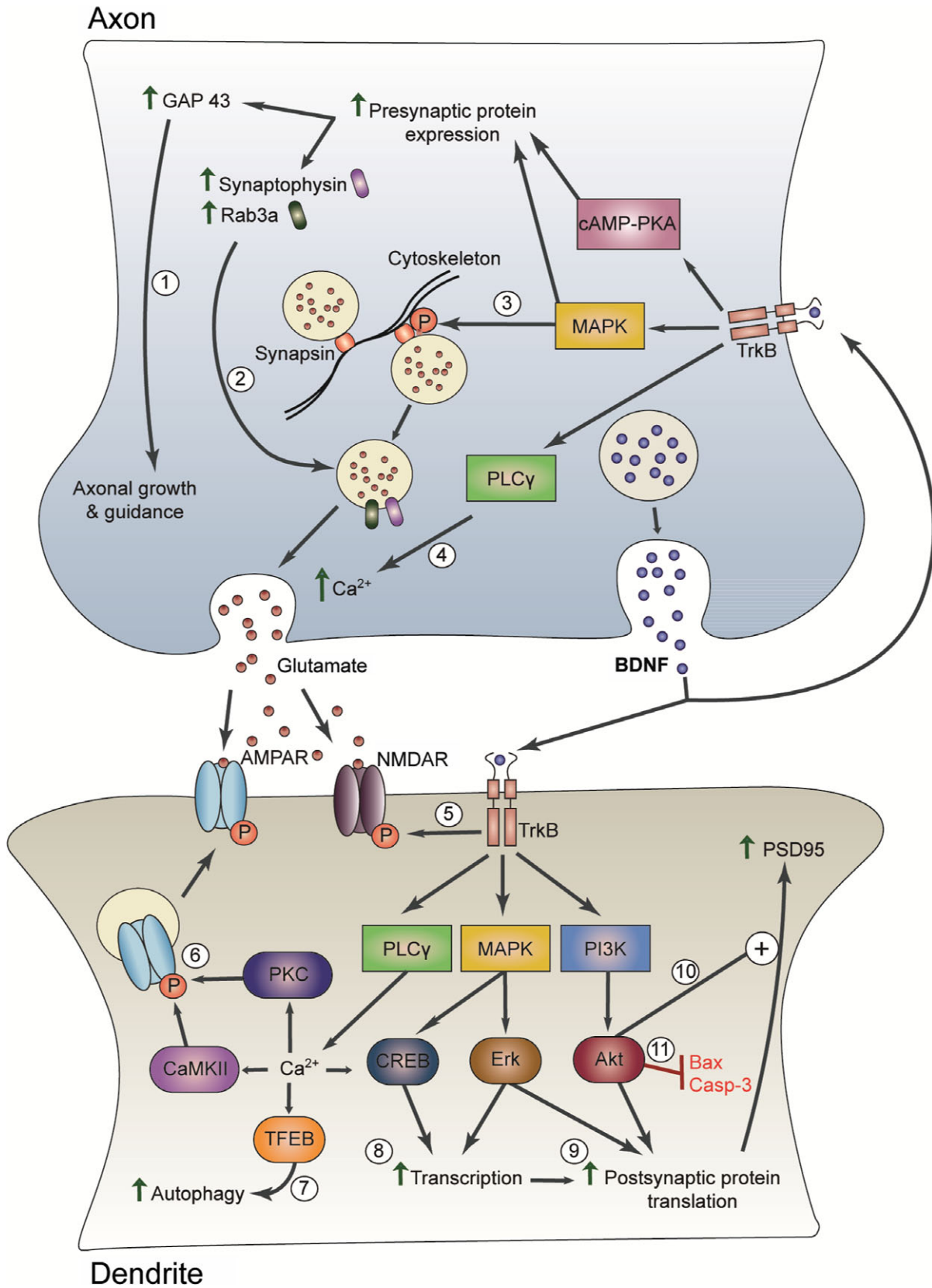
Figure 1. Model of neuroprotective effects of DBS at the synapse. DBS stimulates increased BDNF release which induces structural and functional changes at the synapse by binding pre- and postsynaptic TrkB receptors. At the presynaptic terminal, activation of the cAMP-PKA and MAPK pathways promotes increased presynaptic gene expression including key proteins involved in axonal growth and guidance (e.g. GAP 43) (1) and neurotransmitter vesicle release (e.g. synaptophysin, Rab3a) (2).[90–94] MAPK phosphorylation of synapsin also releases neurotransmitter vesicles from cytoskeleton-bound pools (3).[95] TrkB-mediated activation of PLCγ increases intracellular Ca^{2+} concentration leading to increased presynaptic neurotransmitter release (4).[90] At the postsynaptic terminal, TrkB activation leads to tyrosine phosphorylation of NMDA-type glutamate receptor (NMDAR) subunits, increasing conductance (5).[96,97] Activation of the PLCγ pathway induces a rise in intracellular Ca^{2+} concentration and subsequent activation of Ca^{2+}/calmodulin-dependent kinase II (CaMKII) and protein kinase C (PKC), which phosphorylate AMPA-type glutamate receptors (AMPAR) subunits and increase their delivery to the postsynaptic terminal (6).[98] Elevated Ca^{2+} levels may also activate transcription factor EB (TFEB), which is the major regulator of autophagy and could enhance clearance of toxic misfolded proteins (7).[70,99] TrkB-mediated activation of cAMP response element binding protein (CREB) and Erk enhances gene transcription (8).[25] BDNF-TrkB signaling also enhances postsynaptic protein translation through both MAPK/Erk and PI3K/Akt pathways (9).[25] The PI3K/Akt pathway is also involved in regulating the trafficking of proteins (e.g. PSD95) to the postsynaptic terminal (10)[25] and inhibition of apoptosis (11).[100,101]

of PD patients who received long-term STN-DBS revealed no rescue of SNpc dopaminergic neurons or reduction in α-synuclein burden.[30] The discrepancy between preserved motor scores and continued dopaminergic neurodegeneration could be explained by a prolonged stimulation "wash-out" period, in which DBS has a lasting effect in disrupting pathological oscillatory activity in the basal ganglia after being switched off. In contrast to motor symptoms, patients receiving chronic STN-DBS display continued progression of levodopa-unresponsive features such as axial symptoms, speech disturbance, and cognitive dysfunction, suggesting ongoing progression of the disease in nondopaminergic regions of the brain.[28,31–33]

A limited number of studies have investigated the effect of STN-DBS on survival. In a nonrandomized trial, Ngoga et al. showed improved survival in PD patients who received DBS surgery compared to controls treated with medication alone;[34] however this could be an indirect effect of improved motor function in reducing complications such as aspiration pneumonia. Another study by Lilleeng et al. reported no difference in mortality rates between a cohort of PD patients treated with STN-DBS and a control group treated only with medication.[35] These results must be interpreted with caution since the authors identified control subjects from historical records, raising the possibility that confounding environmental factors affected mortality rates in the two groups.

In the absence of a clear neuroprotective effect in patients, it is important to consider possible limitations of the long-term studies of STN-DBS to date. At the stage of subject enrollment, PD has been treated as a single disorder, despite marked genotypic, and phenotypic heterogeneity between patients. Variation in rates of disease progression between trial subjects creates significant "noise" which can mask treatment effects, particularly within the short time scale of most clinical trials.[36] As an alternative, PD patients could be recruited in stratified cohorts with similar predicated rates of disease progression based on validated biomarkers. A biomarker is

defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention".[37] However, despite intensive study of DNA, RNA, biofluid samples, peripheral tissue sampling, and imaging, no reliable biomarkers have been identified which can predict the trajectory of disease progression in PD patients.[36] In their absence, clinical trials seeking to determine the neuroprotective potential of STN-DBS must compensate for phenotypic heterogeneity by recruiting larger numbers of patients to ensure that there is sufficient statistical power to detect disease-modifying effects.

Another limitation of subject selection in long-term STN-DBS studies to date has been the recruitment of patients with advanced PD when nigral cell death is already well-established. The majority of dopaminergic terminals are lost within 4 years of PD diagnosis,[38] and yet the average STN-DBS surgery takes place 12–15 years after diagnosis.[39] It is therefore unsurprising that evidence of a neuroprotective effect of DBS on SNpc neurons has been lacking.

In choosing clinical trial endpoints to assess the long-term efficacy of STN-DBS, to date there has been no consensus in what constitutes neuroprotection or a disease-modifying effect. To demonstrate that an intervention has modified the natural course of PD, an effect on disease pathogenesis would be expected, such as a reduction in the rate of neuronal loss or alpha-synuclein burden. In the absence of reliable biomarkers which can predict the extent of neurodegeneration *premortem*, trials to date have instead had to rely on clinical assessments of symptom severity.[40] For example, many trials have employed symptomatic rating scales such as the Unified PD Rating Scale (UPDRS) as clinical endpoints. The UPDRS investigates motor symptom severity, behavior, mood, mentation, and ability to perform activities of daily living. The scale is vulnerable to both intra- and inter-rater variability.[41] In addition, any stabilization of the UPDRS in

patients receiving DBS is likely to be confounded by improvements in motor symptoms. Other endpoints used to assess PD progression in trials include time taken for a drug-naïve patient to require dopaminergic therapy, as well as stability of the levodopa equivalent dose (LED) over years.[40,41] However, response to dopaminergic therapy is often considered in determining candidacy for DBS and thus cannot serve as an endpoint to assess if DBS is neuroprotective.[40]

Due to ethical concerns, it will not be possible to compare STN-DBS "on" and "off" conditions using a long-term randomized control trial study design. Instead, long-term follow-up of patients treated with STN-DBS from an early stage of PD[41,42] could give important insights into the neuroprotective potential of DBS in patients with a more intact nigrostriatal system. In the absence of validated biomarkers, it will be necessary to recruit larger numbers of subjects and attempt stratification of subjects into cohorts by their baseline clinical phenotype. Instead of symptom rating scales, future STN-DBS neuroprotection trials would benefit from employing more objective measures of disease progression (e.g. 18F-fluorodopa PET, serial structural magnetic resonance imaging).

Alzheimer's Disease

An estimated 46.8 million people worldwide are living with dementia, with an associated global cost of approximately $818 billion.[43] Alzheimer's disease (AD) is the most common form of dementia, characterized by the widespread accumulation of extracellular amyloid plaques and intraneuronal neurofibrillary tangles (NFTs). Amyloid plaques are composed of an aggregated 40- to 42-residue peptide called beta-amyloid ($A\beta_{1-40}$ and $A\beta_{1-42}$), while the main component of NFTs is a hyperphosphorylated form of tau protein.[44] Recent investigation of DBS as a potential novel treatment for AD was prompted by the serendipitous discovery that stimulation of the fornix resulted in episodic memory recall during DBS electrode implantation for treatment of morbid obesity.[45] Located in the medial diencephalon, the fornix is a critical component of the well-known circuit of Papez. A phase I trial of forniceal DBS in patients with mild AD revealed an improved temporoparietal hypometabolism and a reduction in the expected rate of cognitive decline at 6 and 12 months in some patients.[46] A 1-year follow-up structural MRI study showed an overall reduction in the rate of hippocampal atrophy in DBS-treated AD patients compared to matched AD controls not receiving DBS.[47] The later phase II multi-center double blind randomized controlled ADvance trial of 42 patients with mild AD examined the safety and efficacy of forniceal DBS.[48] Whilst both electrode implantation surgery and subsequent stimulation were well tolerated, no significant difference in primary clinical outcome at 12 months was observed, as measured by AD Assessment Scale cognitive subscale (ADAS-Cog13) and Clinical Dementia Rating scale sum of boxes (CDR-SB) cognitive scores. Patients receiving stimulation displayed elevated glucose metabolism at 6 months, but this effect was not seen at a later 12 month time point. *Post-hoc* analysis revealed a significant interaction between age and clinical outcome, with trends toward improvement in patients over the age of 65 years and worsening in younger patients. These early studies of forniceal DBS suggest that neuromodulation of memory circuits is feasible, well tolerated, and may have the potential to slow disease progression in a subgroup of AD patients over 65 years of age. A planned phase III international multi-centre trial will investigate the potential benefits of forniceal DBS in this age group further.

In addition to the fornix, DBS of the nucleus basalis of Meynert (NBM) in the basal forebrain is being considered as a therapeutic target in patients with AD. The NBM is an important source of acetylcholine supply to the neocortex, and neuronal loss within this region correlates closely with cortical cholinergic deficits and the degree of cognitive impairment in patients with AD.[49] Low-frequency stimulation of the NBM aims to excite residual cholinergic neurons, leading to increased cholinergic transmission to the neocortex.[49] In an initial safety study, four out of six AD patients who received low-frequency NBM-DBS remained stable or showed improvement in cognitive assessment scores after 1 year.[50] Interestingly, patients who respond to NBM-DBS appear to have higher baseline cognitive function[51] and more limited fronto-parieto-temporal cortical atrophy.[52] This suggests that NBM-DBS may slow cognitive decline in patients with early AD by stimulating increased transmission from remaining cholinergic neurons.

Despite early evidence to suggest that forniceal and NBM-DBS may stabilize or even improve cognitive scores in certain patients with mild AD, confirmation of a neuroprotective effect is still lacking. As in PD, electrical stimulation of brain regions involved in memory function may lead to symptomatic improvement in patients with mild AD by temporarily enhancing the formation or retrieval of memories. Whether forniceal or NBM-DBS are associated with lasting cognitive benefits on cessation of stimulation or can limit the rate of disease progression at a neuropathological level remains unclear. In the first instance, it will be important to identify which stimulation parameters are associated with the sustained memory benefit, if any, before assessing any long-term impact on disease progression. Future clinical studies may be guided by evidence from studies in laboratory animals, which have started to

yield important insights into the neuroprotective potential of DBS as a treatment for AD, as discussed below.

Neuroprotection in animal models

Electrical stimulation of the NBM increases cortical acetylcholine release[53] and improves memory function in wild-type rats.[54–56] Increased cholinergic input to the neocortex in response to NBM-DBS induces secretion of nerve growth factor (NGF) by target cortical neurons.[57] This is known to be critical for the survival and function of cholinergic basal forebrain neurons.[58] In addition to enhanced neurotrophic support, NBM-DBS has been shown to increase synaptic plasticity in the cortex of wild-type rats.[59] Further studies are required to determine whether NBM-DBS has similar neuroprotective effects in rodents with established features of AD neuropathology.

Forniceal DBS has also been shown to have beneficial effects on cognitive function in rodents, with reported improvements in spatial,[60–63] contextual,[60] and recognition[63] memory. DBS of the entorhinal cortex (EC) has also been shown to improve spatial[64,65] and contextual[65] memory, suggesting that the pro-cognitive effects of DBS may reflect generic activation of the circuit of Papez. Consistent with this theory, forniceal DBS upregulates activity-dependent cFos gene expression in connected remote areas of the hippocampus within 2–2.5 h of stimulation onset.[66,67] Despite early changes in gene expression, studies of EC-DBS in mice show that improvements in memory can take 3–6 weeks to emerge after a single episode of acute stimulation.[64,65] This temporal lag could reflect gradual structural changes in the hippocampus (e.g. synaptic remodelling, neurogenesis) in response to stimulation-induced neurotrophic factor release.[10,24,66] In support of this hypothesis, DBS of the fornix,[60] EC,[64] and anterior thalamic nucleus[68,69] promote neurogenesis in the dentate gyrus. Moreover, forniceal DBS increases hippocampal expression of synaptophysin and GAP43 in wild-type rats[66] and EC-DBS rescues synaptophysin levels in the triple transgenic mouse model of AD.[70] Both synaptic proteins have important roles in axonal growth and guidance, as well as synaptic plasticity. Akwa and colleagues reported that EC-DBS limits synaptic loss in an AD mouse model by stimulating autophagic-lysosomal clearance of pathological forms of tau protein.[70] These findings are of particular relevance in AD, where synaptic failure is one of the earliest hallmarks of disease and correlates closely with the degree of memory impairment.[71] In addition to tau protein, amyloid plaque load has been shown to be reduced with EC-DBS if initiated at early stages of memory impairment in an AD mouse model.[65]

Early animal studies support a potential neuroprotective role for DBS in the treatment of AD by promoting synaptic plasticity, hippocampal neurogenesis, and increased clearance of misfolded protein conformers. It is, however, important to note some key limitations of these studies. Results from studies of wild-type animals[61,66,67] or pharmacological models of AD[62,63] may not be translatable to AD patients who have evidence of amyloid deposition, widespread synaptic dysfunction, and established neuronal loss at time of diagnosis. In addition, all animal studies to date have employed acute stimulation paradigms (e.g. single 1 h episode), rather than the continuous stimulation protocol currently used in patients. Future studies using standardised chronic stimulation parameters in validated AD animal models may yield important insights into how the neuroprotective effects of DBS could be optimized in future clinical trials.

Epilepsy

Epilepsy is a common neurological disorder characterized by a predisposition to recurrent seizures. Many forms of epilepsy can have profound structural and functional effects on the brain if left untreated. For instance, longitudinal MRI studies of patients with temporal lobe epilepsy (TLE), the most common type of epilepsy in adults, have revealed hippocampal volume loss which correlates with the frequency of generalized seizures, suggesting seizure-associated hippocampal damage.[72,73] TLE is resistant to antiepileptic medications in approximately one third of cases.[74] Surgical resection of an epileptogenic focus can prevent disabling seizures in approximately 65% of these patients.[75] In patients who lack a single epileptogenic focus or have significant medical comorbidities, DBS of the anterior thalamic nucleus (ANT) can be considered as an alternative to resective surgery.[76,77] Whilst long-term follow-up studies of ANT-DBS in patients are currently limited, early evidence from animal models suggests that DBS may have important neuroprotective properties in epilepsy, in addition to improved seizure control.

Neuroprotection in animal models

Kainic acid (KA), a potent agonist of kainic receptors and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)-type receptors, is frequently used to model human TLE due to its ability to induce seizures and associated hippocampal cell death.[78] Chen and colleagues reported that high-frequency hippocampal stimulation reduced seizure frequency and protected against neuronal loss following KA injection in a macaque model of epilepsy.[79] Neuronal rescue was associated with reduced levels of the pro-apoptotic factors Bax and activated caspase-3, and increased levels of the antiapoptotic protein Bcl-2.[79] A similar reduction in seizure frequency and hippocampal

neuronal loss was also reported following DBS targeting the ANT region in KA-induced epileptic monkeys.[80] Several mechanisms have been proposed which could explain this neuroprotective effect. Human and animal models of epilepsy are characterized by acutely and chronically elevated levels of pro-inflammatory cytokines (e.g. TNF-α, IL-1β and IL-6) in affected brain regions.[81] Recent studies by Chen et al. demonstrated that ANT-DBS attenuated this pro-inflammatory cytokine response and reduced neuronal injury following KA administration in rats.[82,83] Dampening neuroinflammation could help to reduce neurotoxicity and limit apoptosis.

In addition to anti-inflammatory effects, DBS may protect neurons by reducing neurotransmitter excitotoxicity. Excessive glutamate levels are believed to contribute to neurotoxicity and neuronal loss in epilepsy.[84] Recently, Shi et al. used microdialysis techniques to show that chronic ANT-DBS reduces glutamate levels and increases levels of the inhibitory neurotransmitters GABA and taurine in KA-induced epileptic monkeys while stimulation was switched on.[85] By reversing the imbalance in neurotransmitter levels, ANT-DBS may help to limit glutamate-induced excitotoxicity in epileptic neuronal networks.

Taken together, early preclinical evidence suggests that ANT-DBS has the potential to limit neurotoxicity associated with recurrent seizures and protect against progressive hippocampal neuronal loss. However, it is important to acknowledge some key technical limitations of the existing studies. Firstly, there has been a lack of consistency in the duration of stimulation (e.g. 12 h vs. 6 months) and species (e.g. rat vs. macaque) used, making it challenging to corroborate findings and to delineate common underlying mechanisms of ANT-DBS. Secondly, reported alterations in cytokine or neurotransmitter levels were measured while ANT stimulation was switched on. As a result, it is not possible to determine whether any reduction in neurotoxicity was a direct effect of stimulation, or secondary to a reduction in recent seizure frequency. Lastly, the promising effects of ANT-DBS on hippocampal neuronal counts must be interpreted with caution since none of the above mentioned studies employed unbiased stereological methods, which are considered to be the "gold standard" in quantitative neuropathology.

Summary and Future Directions

In addition to delivering substantial clinical benefit, evidence from preclinical models suggests that DBS may have a wide range of neuroprotective effects including stimulation of neurotrophic factor release, synaptic remodeling, inhibition of apoptosis, dampening of neuroinflammation, reduction in glutamate excitotoxicity, and enhanced clearance of toxic misfolded proteins. BDNF was recently identified as a critical mediator of the neuroprotective response to DBS[26] and could link many of these pleiotropic effects (Fig. 1). Despite mounting evidence to support a disease-modifying role of DBS in preclinical models of AD, PD, and epilepsy, as discussed above significant variation in the animal species, genetic backgrounds, and stimulation conditions used makes it challenging to draw any definitive conclusions about a potential underlying mechanism. Furthermore given the significant differences between neurodegenerative diseases and respective preclinical models there may be pathology specific variations that determine whether there will be a response to stimulation and by which specific mechanism. Since studies of DBS-mediated neuroprotection in patients necessitate a long follow-up period, it will be critical to continue to study DBS in validated animal models to guide selection of neuroanatomical targets and stimulation parameters associated with optimal neuroprotective properties.

Support for the neuroprotective theory of DBS amongst clinicians has been lacking due to limited evidence of disease-modifying effects in human trials to date. In the clinical setting, DBS is often deployed late in the disease course and thus the "window of opportunity" for neuroprotection may be lost. The therapeutic benefit of DBS is thought to depend on modulation of remote brain regions connected in a neural network with the stimulation site.[86] Since synaptic loss has been implicated in neural network dysfunction,[87,88] the therapeutic potential of DBS is likely to decline with progression of neurodegenerative conditions such as PD and AD. As a result, randomized controlled trials at *early* stages of disease are required to assess the neuroprotective potential of DBS before significant synaptic loss has occurred. Consistent with this approach, a phase III multicenter randomized double-blind placebo controlled trial evaluating the effect of DBS in early PD is currently underway.[41,89] In addition to studying the effects of DBS on earlier stages of disease, future trials would benefit from the discovery of reliable disease biomarkers, which can predict the extent of disease progression (e.g. biofluid or serial structural/volumetric MRI markers). These could help to minimize heterogeneity between subjects at the time of trial recruitment and could also be used as trial endpoints to determine if DBS can slow the rate of disease progression, independent of any effect on symptom severity scores.

Disclosures

Conflict of Interest

None.

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