Stimulate or Degenerate: Deep Brain Stimulation of the Nucleus Basalis Meynert in Alzheimer Dementia

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Key words
- Alzheimer disease
- Deep brain stimulation
- Nerve growth factor

Abbreviations and Acronyms
ACh: Acetylcholine
AD: Alzheimer dementia
BFA: Basal forebrain area
BFCN: Basal forebrain cholinergic neurons
DBS: Deep-brain stimulation
MCI: Mild cognitive impairment
NBM: Nucleus basalis Meynert
NGF: Nerve growth factor

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OBJECTIVE: **Deep brain stimulation (DBS) is a therapeutically effective neurosurgical method originally applied in movement disorders. Over time, the application of DBS has increasingly been considered as a therapeutic option for several neuropsychiatric disorders, including Gilles de la Tourette syndrome, obsessive compulsive disorder, major depression and addiction. Latest research suggests beneficial effects of DBS in Alzheimer dementia (AD). Because of the high prevalence and the considerable burden of the disease, we endeavored to discuss and reveal the challenges of DBS in AD.**

METHODS: **Recent literature on the pathophysiology of AD, including translational data and human studies, has been studied to generate a fundamental hypothesis regarding the effects of electrical stimulation on cognition and to facilitate our ongoing pilot study regarding DBS of the nucleus basalis Meynert (NBM) in patients with AD.**

RESULTS: **It is hypothesized that DBS in the nucleus basalis Meynert could probably improve or at least stabilize memory and cognitive functioning in patients with AD by facilitating neural oscillations and by enhancing the synthesis of nerve growth factors.**

CONCLUSIONS: **Considering the large number of patients suffering from AD, there is a great need for novel and effective treatment methods. Our research provides insights into the theoretical background of DBS in AD. Providing that our hypothesis will be validated by our ongoing pilot study, DBS could be an opportunity in the treatment of AD.**

DEEP BRAIN STIMULATION (DBS)

Since the late 1980s, DBS has substantially expanded the therapeutic possibilities of treating movement disorders such as Parkinson disease (7, 8). DBS refers to a complex neuromodulative procedure in which electrodes are stereotactically implanted into defined target structures of the brain. Despite many years of experience with DBS, the therapeutic effects are not yet well understood. There are various mechanisms of action being discussed, such as excitatory and inhibitory actions on the next processing stage (57, 58) or interactions with neuromodulators or receptors. The benefit of DBS in the field of movement disorders has repeatedly been documented, and the minimal invasiveness of the procedure and the rare and usually minor side effects open the implementation of DBS for other neurological and psychiatric indications (41). Along this line, the results of various studies have pointed out promising effects of DBS for the treatment of severe obsessive compulsive disorder, Tourette syndrome and major depression (35, 40, 48, 64, 68, 90). In the last 2 years, two investigations have even been published in which DBS has been used with the aim to improve cognitive abilities in patients with dementia (27, 50). Furthermore, improved memory processing in patients not affected by dementia has just recently been described (31, 82).

In this context a new target candidate is the nucleus basalis Meynert (NBM; see http://clinicaltrials.gov/ct2/show/NCT01094145). Theodor Meynert's neuroanatomic studies contributed to the development of the nineteenth-century "brain psychiatry" movement. His speculation that certain cognitive impairments resulted from an imbalance in blood flow between cortical and subcortical structures parallels modern controversies concerning the role of these brain regions in the pathophysiology of dementia. Meynert described a subcortical nucleus in the basal forebrain, the nucleus basalis of Meynert (i.e., NBM), which has been shown to provide cholinergic innervation to the cortex. Loss of cells within this structure may account for the loss of cortical cholinergic markers in Alzheimer disease (AD), a so-called "cortical" dementia, and in the dementia of Parkinson disease. The article by Whitehouse et al. revived the concept of a pivotal role of the NBM for the pathogenesis of AD (96).

An influential electrophysiological study (16) forwarded the concept that increased neuronal firing of the NBM provides a steady background of neocortical activity that may enhance the effects of other afferents to the neocortex (78). Thereby, the more general action of the NBM on the cortex was regarded as an analogue to the classical concept of Moruzzi and Magoun, who envisaged the reticular ascending fiber system as an arousal system (65). Since then, ample experimental evidence has been accumulated supporting the role of the NBM for cortical tuning and the consequences of the breakdown of this action by degeneration of this nucleus in the earliest stages of dementia.

Specific modifications of NBM stimulation on cortical processing have also been demonstrated. Episodic electrical stimulation of the nucleus basalis, paired with an auditory stimulus, accomplished massive and progressive reorganization of the primary auditory cortex in the adult rat that also outlasted stimulation for hours and suggested that the basal forebrain plays an active instructional role in representational plasticity (45).

The wealth of experimental data provides the background for clinical applications that try to modify NBM function by either molecular or electrical neuromodulative methods. The objective of this article is a state-of-art discussion of the current rational for this type of approach. Neuromodulation of the basal forebrain structures could open a new avenue for compensating for subcortical dysfunctions that characterize degenerative diseases by modifying cortical functions, and may even provide some insight into the pathophysiology and pathogenesis of AD.

ALZHEIMER DEMENTIA

AD is characterized by a chronic progressive cognitive deterioration, frequently accompanied by psychopathological symptoms, reduced functional ability, changes in personality, social isolation and loss in quality of life. With a proportion of 70%–80%, AD is the most prevalent form of dementia and, because of its limited treatment options, a severely disabling disorder not only for the patient concerned but also for the relatives providing care (26, 79).

Besides a polygenetic predisposition, multifactorial causes contribute to the development of AD. Despite great efforts, so far no scientific consensus of a convergent concept about the neurobiological processes in AD has been achieved. The most frequently cited idea is the "amyloid cascade hypothesis," which states that the extracellular formation and aggregation of β-amyloid peptides, so-called cerebral amyloid plaques, and the synthesis of intracellular neurofibrillary bundles of hyperphosphorilated tau proteins are the initial steps in the development of AD and eventually result in the elective inexorable atrophy of neurons (20, 44, 71). Based on the amyloid cascade hypothesis, some modern therapeutic approaches focus on preventing or reversing the formation of amyloid, including active and passive immunization against β-amyloid (51, 83). Unfortunately, up to now this treatment approach could not achieve sustained success.

The lack of an effective treatment is all the more disappointing as a major progress has been made regarding diagnostic procedures over the past years. Detecting and diagnosing the disease earlier is now possible by the detection of amyloid deposition through positron emission tomography (PET), cerebrospinal fluid markers, and the clinical concepts of mild cognitive impairment (MCI) and pre-MCI (19, 24, 81, 94).

Until now, the treatment of choice is still based on the administration of antidementive medication such as memantine, donepezil, galantamine or rivastigmine (95). Although their positive effect on cognitive abilities in patients with AD is unquestioned, effect sizes (d) are rather small and vary between 0.1 and 0.4 (6, 23, 62). With the exception of memantine (an NMDA glutamate receptor antagonist), all substances modify the inhibition of cholinesterase.

The approach to treat AD by enhancing cholinergic functioning originated in the cholinergic hypothesis by Bartus et al. (6), who states that the development of AD is a response to a reduced synthesis of acetylcholine (ACh) caused by the progressive neuronal degeneration.

ACh is essential for cognitive functioning and memory processing. The release of ACh is voltage-dependent and mediated through the initiation of action potentials. The disposal of ACh is carried out in parcels of 10,000 molecules. The postsynaptic excitation through ACh triggers a complex intracellular signaling cascade (25), which is based on a subtle interplay between muscarinic and nicotinic postsynaptic receptor activation (23, 33, 62). It could be demonstrated that an elevation of ACh levels in healthy adults as well as in demented patients enhances memory capacity and improves performance on several cognitive tasks including verbal and object learning (38, 62, 63).

In more detail, Kukolja et al. (49) could show that nicotinergic stimulation with physostigmine facilitates encoding of spatial contextual information and is associated with increased neural activity in the right hippocampal formation. In addition, it could be demonstrated that participants who were worse at the baseline examination benefited more from cholinergic stimulation than participants with better baseline scores on a test assessing cognitive functioning. Bearing this in mind, it can be assumed that reduced ACh levels impair cognitive functioning not only in patients with dementia but even in healthy subjects. The witnessed correlation of cognitive functioning and the level of ACh has also been emphasized by other investigations: If the cholinergic transmission is blocked in humans and monkeys, cognitive abilities are reduced in a similar way as they are in patients with mild and moderate AD (5, 10). Furthermore, it appears that the severity of the symptoms in dementia is dependent on the level of cholinergic loss and that vice versa the treatment with antidementive medication and cholinergic modulators improves the symptoms of AD (10, 12, 15). The principle sources of ACh are the cholinergic neurons in the basal forebrain, wherefrom cholinergic fibers project to all layers of the neocortical mantle and to the hippocampus and amygdala (18). Apart from this, there are cholinergic interneurons in the striatum.

THE BASAL FOREBRAIN AREA AND THE NBM

The basal forebrain area (BFA) has a complex architecture (60). It comprises the basal forebrain cholinergic neurons (BFCN) within the medial septal nucleus, the diagonal band nucleus and the nucleus basalis of Meynert (NBM) (**Figure 1**). The NBM, also termed CH4 group, has the largest volume. It could be demonstrated that approximately 90% of