Doctoral thesis

Curriculum Vitae

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Neurostimulation for refractory epilepsy

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Abstract

Neurostimulation is an emerging treatment for refractory epilepsy. To date the precise mechanism of action remains to be elucidated. Better insight in the mechanism of action may identify seizure types or syndromes that respond to such a treatment and may guide the search for optimal stimulation parameters and finally improve clinical efficacy. In the past ten years some progress has been made through neurophysiological, neuroanatomical, neurochemical and cerebral blood flow studies in patients and animals undergoing vagus nerve stimulation (VNS). Interesting results have been found in VNS-treated patients that underwent evoked potential measurements, cerebrospinal fluid investigation, neuropsychological testing and PET, SPECT and fMRI testing. Desynchronisation of abnormal synchronous epileptic activity is one of the hypotheses on the mode of action that might primarily be responsible for an anti-seizure effect. There is however increasing evidence from research and clinical observation that VNS might establish a true and long-term anti-epileptic effect. It has been shown that VNS influences neurotransmission in the brain and provokes long-term changes in cerebral blood flow in areas crucial for epileptogenesis such as the thalamus and medial temporal lobe structures. Deep brain stimulation (DBS) for epilepsy has regained interest. Central nervous system structures known to play a key role in the epileptogenic network such as the thalamus and subthalamic nucleus have been targeted. Another approach is to target the ictal onset zone such as the medial temporal lobe. At Ghent University Hospital 10 patients have been treated with long-term amygdalohippocampal DBS. Several hypotheses have been raised for the mechanism of action of DBS for refractory seizures. Seizure reduction may be due to a microlesion caused by electrode insertion or by provoking a reversible functional lesion due to the effect of electrical current on hyperexcitable tissue. Neurophysiological techniques such as evoked potentials monitoring and intraoperative single unit potential recordings may guide correct electrode placement, individual DBS titration and elucidation of the mechanims of action of DBS for epilepsy.

Introduction

Up to 30% of patients with epilepsy have uncontrolled seizures despite adequate treatment with antiepileptic drugs (AEDs) (1). The treatment options for these patients in specialised epilepsy centers include trials with newly developed antiepileptic drugs, disconnective or resective epilepsy surgery, the ketogenic diet or neurostimulation.

Neurostimulation is an emerging treatment for neurological diseases. Electrical pulses are administered directly to or in the neighbourhood of nervous tissue in order to manipulate a pathological substrate and to achieve a symptomatic or even curative therapeutic effect. Different types of neurostimulation exist mainly depending of the part of the nervous system that is being affected and the way this stimulation is being administered (Fig. 1).

Electrical stimulation of the tenth cranial nerve or *vagus nerve stimulation (VNS)* is an extracranial form of stimulation that was developed in the eighties and is currently routinely available in epilepsy centers around the world. Through an implanted device and electrode, electrical pulses are administered to the afferent fibers of the left vagus nerve in the neck. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment (2). As stimulation is applied to that part of the vagus nerve that passes through the neck, direct intracerebral manipulation is unnecessary.

Another form of extracranial neurostimulation consists of *transcranial magnetic stimulation (TMS)*. A coil that transmits magnetic fields is held over the scalp and allows a non-invasive evaluation of separate excitatory and inhibitory functions of the cerebral cortex. In addition, repetitive TMS (rTMS) can modulate the excitability of cortical

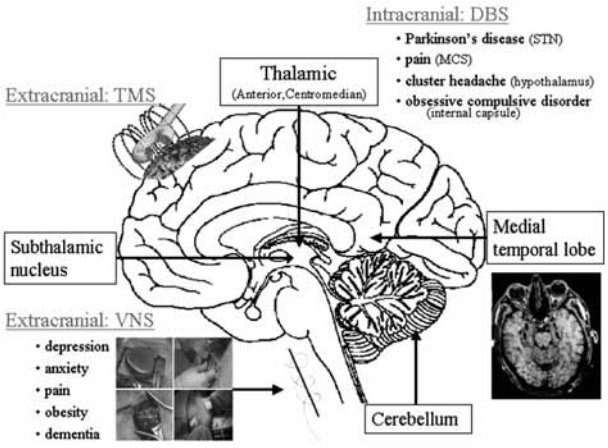

Fig. 1. — Different neurostimulation modalities.
Legend : TMS : transcranial magnetic stimulation, DBS : deep brain stimulation, STN : subthalamic nucleus, MCS : motor cortex stimulation.

networks (3). This therapeutic form of TMS is currently being investigated as a treatment option for refractory epilepsy but it has not been widely used unlike VNS.

Intracerebral neurostimulation requires accessing the intracranial nervous system as stimulation electrodes are inserted into intracerebral targets for *'deep brain stimulation' (DBS)* or placed over the cortical convexity for *'cortical stimulation' (CS)*. These modalities of neurostimulation are not novel for neurological indications. Some have been extensively used e.g. for movement disorders and pain (4, 5). Moreover several new indications such as obsessive compulsive behaviour and cluster headache are being investigated with promising results (6, 7). In the past, DBS and CS of different brain structures such as the cerebellum, the locus coeruleus and the thalamus have already been performed. This was done mostly in patients with spasticity or psychiatric disorders who also had epilepsy but the technique was not fully explored or developed into an efficacious treatment option (8-11). The vast progress in biotechnology along with the experience in other neurological diseases in the past ten years has led to a renewed interest in intracerebral stimulation for epilepsy. A few epilepsy centers around the world have recently reinitiated trials with deep brain stimulation in different intracerebral structures such as the thalamus, the subthalamic nucleus and the caudate nucleus (12-16).

Vagus nerve stimulation

Clinical efficacy and side effects

Vagus nerve stimulation (VNS) consists of intermittent stimulation of the left vagal nerve by means of an implanted stimulation electrode and pulse generator. In 1988, VNS was first used in a patient and in 1997, following two randomized double blind controlled studies showing short term efficacy and safety of VNS, the FDA (Food and Drug Administration, U.S.A.) approved this treatment (2). Since then, an increasing number of patients have been treated with VNS. This new treatment modality for epilepsy is usually prescribed as an add-on treatment to ongoing antiepileptic drugs.

At the Reference Center for Refractory Epilepsy in Ghent University Hospital, the first patients were treated with VNS in 1995. When prospective data became available on 15 patients, who had been followed for at least 6 months, a detailed efficacy and safety analysis was made (17). A second analysis was performed in December 2000 when 35 patients had reached a follow-up of at least 9 months (18). By February 2003, the number of treated patients had increased up to 73. Sixty-one patients had a follow-up of at least 6 months. The data from these patients were analyzed, compared and pooled with patient data from 57 patients treated for at least 6 months at the epilepsy center of Dartmouth Hitchcock Medical Center in the U.S.A. (19). Specific aspects that were investigated in these patients included efficacy and safety after long-term treatment, seizure freedom, efficacy of the magnet feature and replacement of the generator when battery expiration is reached.

In the first study a mean reduction in seizure frequency of 42% was found after a mean follow-up of 2.5 years. The second analysis showed a mean reduction in seizure frequency of 63%. In the third study there was a mean follow-up of 3 years in 118 patients from two centers. The mean reduction in seizure frequency was 55%. In these studies, we evaluated the reduction in seizure frequency with regards to seizure type. Generalized and partial seizures responded equally well to VNS. Simple partial seizures had a tendency to respond especially well to VNS. In the patient group treated at Ghent University Hospital, 6 patients were diagnosed with Lennox-Gastaut Syndrome. In these patients a mean reduction of 59% (range : 0-90%) in seizure frequency was found.

In the total group of 118 patients, 8% of the patients experienced long-term seizure freedom. In the first 15 implanted patients, there was a significant increase in the mean seizure-free interval from 9 to 312 days. The different analyses showed that seizure control is maintained over several years of treatment. Analysis of the clinical characteristics, seizure type(s), results of EEG and imaging studies in the responders and especially in the seizure-free patients did not reveal consistent findings with regard to predictive factors for seizure control.

VNS consists of continuous (24/24 hour) but intermittent (standard duty cycle : 30s on, 300-600s off) stimulation. Despite the use of lower pulse

width in the Dartmouth series and lower duty cycles in the Ghent series comparable efficacy was achieved. This leads to interesting findings with regards to saving battery life without diminishing seizure control. Non-responders in our patient series were changed to a rapid cycling scheme (duty cycle 7 s on/14 s off) after 6 months of treatment. This did not result in immediate seizure reduction but in patients who remained on the rapid cycle protocol for several months, improved seizure control was noted. The mean number of AEDs before and after VNS remained unchanged in both centers.

The pure antiseizure effect of VNS has practical applications with regard to the magnet feature. The magnet allows patients with auras to administer an additional stimulation train in order to abort an upcoming seizure. The magnet may also allow a family member or caregiver to interrupt an ongoing seizure. It was unknown what proportion of patients made use of this feature and how efficacious an acutely delivered stimulation train is able to suppress seizures. In a group of 35 patients, sixty percent of the patients reported to use the magnet (18). One third of these patients reported no benefit from the magnet. Two thirds reported a positive effect of magnet use. Three patients were able to abort seizures themselves. Caregivers reported interruption of complex partial seizures and secondary convulsions. More than half of the patients who benefited from the magnet early on in the treatment, eventually became responders. These results suggest that the magnet is a useful tool that provides patients and caregivers with an additional means of controlling refractory seizures. Studies identifying patients in whom the anti-seizure effect of VNS is consistent may lead to the development of ultimate applications such as closed-loop systems. These systems couple seizure prediction algorithms to acute seizure countermeasures such as stimulation. This could obviate the need for continuous treatment which, in the case of VNS, would substantially increase battery life.

Despite the fact that there are indications for VNS-induced long-term changes in the central nervous system, VNS is considered a symptomatic treatment. This implies the need for battery replacement when end of service of the device is reached, usually between 4-12 years depending on the implanted generator model. Currently, there are no guidelines or reports in the literature concerning the indications and optimal timing for generator replacement.

In a patient group at Ghent University Hospital generator replacement was performed at different times following end of service (20). We analysed the different approaches in these patients retrospectively and correlated the findings with seizure control before and after generator replacement. The most relevant findings were that the occurrence of end of service is unpredictable and varies extremely between patients probably because different combinations of stimulation parameters and lead impedance values over several years had been used. End of service may be indicated by a gradual increase in seizure frequency, the sensation of irregular stimulation by the patients or even by the loss of beneficial effects such as improving depressive symptoms. The most striking finding was that loss of seizure control could not always be regained, even after long-term treatment with the second generator. Especially patients who had experienced several months without stimulation were at risk.

In our patient group we have noticed that the typical stimulation-related side effects are present during the first months of treatment during which output current is being gradualy increased. After long-term follow-up only 8/61 patients in the Ghent series and 5/57 patients in the Dartmouth series reported stimulation-related hoarseness (19). In one of the patients treated at Dartmouth intraoperative bradycardia occurred during device testing. Implantation was continued and no similar side effects occurred during ramping up of the output current. One patient had continued postoperative hoarseness due to a vocal cord paralysis that recovered spontaneously after a few weeks. In two patients in our series, one non-responder and one responder, the generator and the electrodes had to be explanted due to a delayed-onset local infection. We have observed psychiatric side effects in 4 patients (21). In three patients this occurred without a history of psychosis and unrelated to seizure control suggesting that the phenomenon of forced normalization was not a major factor. Temporary treatment with antipsychotic drugs resolved this side effect in all patients. In our patient series one patient gave birth to a healthy baby. A second patient is currently in the third trimester of pregnancy with no specific pregnancy problems being reported sofar. Improved mood or cognition has not been investigated with validated QOL or neuropsychological testing in our patient groups. However, many patients or caregivers report increased alertness and/or mood.

Mechanism of action

The precise mechanism of action by which VNS exerts is antiepileptic effect has not been elucidated. Through stimulation of the vagal afferent fibers in the neck, a large number of intracerebral structures are potentially affected. The vagus nerve mainly projects to the nucleus of the solitary tract in the brainstem and consequently has many subcortical and cortical connections that are known to play an important role in the pathophysiology of epilepsy. A better insight in the mechanism of

action may help to identify specific epilepsy syndromes or types of epilepsy that respond well to VNS, a major issue that has not been resolved.

Using functional imaging techniques in patients treated with VNS, we have investigated whether electrical stimulation of the left vagus nerve induces changes in regional cerebral blood flow that were potentially related to the mechanism of action of VNS. Significant changes were found using single photon emission tomography, following an initial 30-second stimulation train (22). The imaging studies were performed at different times during VNS treatment and the results were correlated with long-term clinical efficacy (23). In this way, we have identified the crucial role of the thalamus and the limbic system in the mechanism of action of VNS. In these structures, different VNS-induced cerebral blood flow changes were found following acute and chronic stimulation suggesting the combination of an antiseizure as well as an antiepileptic effect. Correlation of pre-VNS functional imaging with long-term clinical outcome could not identify predictive factors for positive outcome. However long-term outcome was correlated with changes in limbic cerebral blood flow after an initial 30-second stimulation train. This finding may be of use to identify responders before patients are implanted with a permanent device. This would imply the application of functional imaging techniques in patients in whom the vagus nerve is transcutaneously stimulated eg. with the use of transcutaneous electrical nerve stimulation or (TENS) devices.

Another useful approach to investigate the mechanism of action of VNS and provide fast feedback relevant to the clinical situation, is to use animal models for specific types of epilepsy. GAERS (genetic absence epilepsy rats from Strassbourg) provide such a model and were used to explore VNS efficacy in a genetic model of primary generalized epilepsy (24). Initial neurophysiological studies in this specific animal model has shown that absence seizures do not respond to short-term stimulation and that an ongoing seizure reflected by spike and wave discharges on the electroencephalogram cannot be acutely interrupted. Long-term follow-up studies are currently being undertaken as it appears from clinical case reports that especially in absence seizure VNS exerts it anti-epileptic effect only after several months of treatment (25).

Deep brain stimulation

Deep brain stimulation is a different neurostimulation modality that is currently under investigation in patients with refractory epilepsy. Two approaches for DBS in refractory epilepsy can be followed. One approach is to target crucial central nervous systems structures that are considered to have a ‘pacemaker’ or essential role in the epileptogenic network that has been identified such as the thalamus or the subthalamic nucleus. Another approach is to interfere with the area of ictal onset itself. This implies the identification of the ictal onset zone, a process that sometimes requires implantation with intracranial electrodes. In an initial pilot trial we have investigated the latter approach (26). This study investigated two initial but essential steps for the further development of DBS as a potential treatment for a larger patient group with refractory epilepsy. We have therefore studied the feasibility of recording intracranial EEG activity for localizing purposes and subsequent long-term DBS of the identified ictal onset zone using the same electrodes. In this way an additional invasive procedure for the patients is avoided and the anatomical accuracy of the stimulation is guaranteed. The feasibility of using chronic DBS electrodes for the localisation of the ictal onset zone prior to DBS to avoid an additional invasive procedure was confirmed by our study. We were able to show that short-term DBS decreases interictal epileptic activity without causing neuropsychological or other side effects. In a more chronic set-up we were able to demonstrate that DBS of the amygdalohippocampal region decreases seizure frequency and is safe in the long-term. The initial results of this open pilot trial show that DBS is potentially efficacious and safe treatment for patients with refractory epilepsy.

Conclusion

Vagus nerve stimulation is an efficacious and safe treatment for patients with refractory epilepsy. The thalamus and limbic system have been identified as crucial structures in the mechanism of action that may be based on a combined antiseizure and anti-epileptic effect. Identification of responders and optimization of stimulation parameters may further increase response rates. Deep brain stimulation of the ictal onset zone may become a valuable alternative for patients who are unsuitable candidates for epilepsy surgery. Controlled and multicenter studies in larger patient groups are warranted.

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