The Mechanism of Action of Vagus Nerve Stimulation Therapy

a report by

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The inability to adequately treat all patients with refractory epilepsy provides a continuous impetus to investigate novel forms of treatment. Neurostimulation is an emerging treatment for neurological diseases. Electrical pulses are administered directly to, or in the surrounding area of, nervous tissue in order to manipulate a pathological substrate and to achieve a symptomatic or even curative therapeutic effect. Electrical stimulation of the 10th cranial nerve, or vagus nerve stimulation (VNS), is an extracranial form of neurostimulation that was developed in the 1980s.1 In the past decade it has become a valuable option in the treatment of refractory epilepsy.2

Since the first human implant of the VNS Therapy™ device in 1989, over 50,000 patients have been treated with VNS worldwide. As with many antiepileptic treatments, the clinical application of VNS preceded the elucidation of its mechanism of action (MOA). Following a limited number of animal experiments in dogs and monkeys investigating safety and efficacy, the first human trial was carried out.2 One-third of patients with refractory epilepsy treated with VNS were responders and 7–8% became seizure-free.3 It remains unclear what type of epileptic seizures or syndromes respond optimally to VNS. Elucidation of the MOA may improve clinical outcome, as it may provide strategies for the optimisation of stimulation parameters and the identification of suitable VNS candidates.

The Anatomical Basis of Vagus Nerve Stimulation

The vagus nerve is a mixed cranial nerve that consists of ~80% afferent fibres originating from the heart, aorta, lungs and gastrointestinal tract and ~20% efferent fibres that provide parasympathetic innervation of these structures and also innervate the voluntary striated muscles of the larynx and pharynx.4,5 Somata of the efferent fibres are located in the dorsal motor nucleus and nucleus ambiguus. Afferent fibres have their origin in the nodose ganglion and primarily project to the nucleus of the solitary tract. At the cervical level the vagus nerve mainly consists of small-diameter unmyelinated C-fibres (65–80%), with a smaller portion of intermediate-diameter myelinated B-fibres and large-diameter myelinated A-fibres. The nucleus of the solitary tract has widespread projections to numerous areas in the forebrain, as well as the brainstem, including important areas for epileptogenesis such as the amygdala and thalamus. There are direct neural projections into the raphe nucleus, which is the major source of serotonergic neurons, and indirect projections to the locus coeruleus and A5 nuclei, which contain noradrenergic neurons. Finally, there are numerous diffuse cortical connections.

The diffuse pathways of the vagus nerve mediate important visceral reflexes such as coughing, vomiting, swallowing and control of blood pressure and heart rate. Heart rate is mostly influenced by the right vagus nerve, which has dense projections primarily to the atria of the heart.7

Relatively few specific functions of the vagus nerve have been well characterised. The vagus nerve is often considered to be protective, defensive and relaxing. This primary function is exemplified by the lateral line system in fish, the early precedent of the autonomic nervous system.8 The control of homeostatic functions by the central nervous system in these earlier life forms was limited to the escape and avoidance of perturbing stimuli or suboptimal conditions. Its complex anatomical distribution has earned the vagus nerve its name, as ‘vagus’ is the Latin word for wanderer. These two facts together inspired Andrews and Lawes to suggest the name ‘great wandering protector’.8

How to Investigate the Mechanism of Action of Vagus Nerve Stimulation

The basic hypothesis of the MOA was based on the knowledge that the 10th cranial nerve afferents have numerous projections within the central nervous system and that, in this way, action potentials generated in vagal afferents have the potential to affect the entire organism.9 To date, the precise MOA of VNS and how it suppresses seizures remains to be elucidated. Crucial questions with regard to the MOA of VNS occur at different levels.

Nerve Fibres, Central Nervous System Structures and Neurotransmitters

VNS aims to induce action potentials within the different types of fibres that constitute the nerve at the cervical level. The question remains: which fibres are responsible and/or necessary for its seizure-suppressing effect? Unidirectional stimulation, activating afferent vagal fibres, is preferred, as epilepsy is considered a disease with cortical origin, and efferent stimulation may cause adverse effects. The next step is to identify central nervous system structures located on the anatomical pathways from the cervical part of the vagus nerve up to the cortex that play a functional role in the MOA of VNS. These could be central gateway or pacemaker function structures such as...
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the thalamus, or more specific targets involved in the pathophysiology of epilepsy such as the limbic system, or a combination of both. Another issue concerns the identification of the potential involvement of specific neurotransmitters. The intracranial effect of VNS may be based on local or regional gamma aminobutyric acid (GABA) increases or glutamate and aspartate decreases, or may involve other neurotransmitters that have been shown in the past to have a seizure threshold-regulating role, such as serotonin and norepinephrine.10

Antiseizure, Antiepileptic and Antiepileptogenic Treatments

When considering the efficacy of a given treatment in epilepsy, a certain hierarchical profile of the treatment can be distinguished. A treatment can have pure antiseizure effects, meaning that it can abort seizures. To confirm such an effect the treatment is most often administered during an animal experiment in which the animals are injected with a proconvulsant compound followed by the administration of the treatment under investigation. A treatment may provide a true preventative or so-called antiepileptic effect. Antiepileptic efficacy implies that a treatment can prevent seizures, as the main characteristic of the disease, namely the unexpected recurrence of seizures, is prevented from happening. A treatment can also have an antiepileptogenic effect. This implies that the treatment reverses the development of a pathological process that may have evolved over a long period of time. Such a treatment is clearly protective and may even be used for other neuroprotective purposes.

Research Investigating the Mechanism of Action of Vagus Nerve Stimulation

Research directed towards investigating the antiseizure, antiepileptic and potential antiepileptogenic properties of VNS, as well as towards the identification of involved fibres, intracranial structures and neurotransmitter systems, has been carried out. Animal experiments and research in humans treated with VNS have comprised electrophysiological studies (electroencephalogram [EEG], electromyogram and evoked potential), functional anatomical brain imaging studies (positron emission tomography, single proton emission computed tomography [SPECT], functional magnetic resonance imaging, c-fos and densitometry), neuropsychological studies and behavioural studies. Also from the extensive clinical experience with VNS, interesting clues concerning the MOA of VNS have arisen. More recently, the role of the vagus nerve in the immune system has been investigated.

Nerve Fibres, Central Nervous System Structures and Neurotransmitters

From the extensive body of research on the MOA, it is now assumed that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibres.11,12 Unilateral stimulation affects both cerebral hemispheres, as shown in several functional imaging studies.13-15 Brainstem and intracranial structures have been identified and include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic structures.16-19 Neurotransmitters playing a role may involve the major inhibitory neurotransmitter GABA, but also serotonergic and adrenergic systems.19,20 More recently, Neece et al. found that VNS following experimental brain injury in rats protects cortical GABAergic cells from death.21 A SPECT study in humans before and after one year of VNS showed a normalisation of GABA_A receptor density in the individuals with a clear therapeutic response to VNS.22 Follesa et al. showed an increase of norepinephrine concentration in the prefrontal cortex of the rat brain after acute VNS.24 An increased norepinephrine concentration after VNS has also been measured in the hippocampus25 and amygdala.26 Currently, VNS as a neuroimmunomodulatory treatment is being explored. As the vagus nerve plays a critical role in the signalisation and modulation of inflammatory processes, the so-called anti-inflammatory pathway, this could represent a new modality in the MOA of VNS for epilepsy.27,28 Recent experiments have shown that VNS significantly increases cortisol levels in freely moving rats.29

Antiseizure, Antiepileptic and Antiepileptogenic Treatments

Early animal experiments in acute seizure models suggested an antiseizure effect of VNS. McLachlan found that applying VNS at the beginning of a pentylenetetrazole (PTZ)-induced seizure significantly shortened the seizure.30 Woodbury and Woodbury described the beneficial effect of VNS in preventing or reducing PTZ-induced clonic seizures and electrically induced tonic-clonic seizures in rats.31 Zabara found that VNS interrupts or abolishes motor seizures in canines induced by strychnine.32 In our own group, VNS significantly increased the seizure threshold for focal motor seizures in the cortical stimulation model.33 Also in the literature on humans, there is clear evidence of an acute abortive effect of VNS. The magnet feature allows a patient to terminate an upcoming seizure.34 In addition, a few case reports describe the use of VNS for refractory status epilepticus in paediatric and adult patients.35,36

However, in the clinical trials with VNS, many patients did not regularly self-trigger the device at the time of a seizure and still showed good response to VNS. In addition, VNS is administered in an intermittent way, and it appears that seizures occurring during the VNS off-time are also affected. This intermittent method of stimulation is insufficient to explain the reduction of seizures on the basis of abortive effects alone and suggests a true preventative or so-called antiepileptic effect of VNS. The fact that VNS influences seizures at a time when stimulation is in the off-mode has also been shown in many animal and human experiments. In 1985 Zabara reported that seizure control was extended well beyond the end of the stimulation period. Stimulation for one minute could produce seizure suppression for five minutes in canines.37,38 Naitoku and Mikels showed that VNS pre-treatment during one and 60 minutes, prior to administration of the seizure-triggering stimulation, significantly reduced the duration of behavioural seizures and the duration of afterdischarges in amygdala kindled rats.39 In a study by Takaya et al. VNS was discontinued before induction of PTZ seizures that were significantly shortened in duration.40 In addition, repetition of stimuli increased VNS efficacy, suggesting that efficacy of intermittent stimulation improves with long-term use. Zagon and Kemery found that VNS-induced slow hyperpolarisation in the parietal cortex of the rat outlasted a 20-second VNS train by 15 seconds.11 McLachlan found that interictal spike frequency was significantly decreased in patients with VNS under investigation. A treatment may provide a true preventative or so-called antiepileptic effect of VNS. The fact that VNS prevents or reduces PTZ-induced clonic seizures and electrically induced tonic-clonic seizures in rats.31 Zabara found that VNS interrupts or abolishes motor seizures in canines induced by strychnine.32 In our own group, VNS significantly increased the seizure threshold for focal motor seizures in the cortical stimulation model.33 Also in the literature on humans, there is clear evidence of an acute abortive effect of VNS. The magnet feature allows a patient to terminate an upcoming seizure.34 In addition, a few case reports describe the use of VNS for refractory status epilepticus in paediatric and adult patients.35,36

The fact that seizures reoccur after the end of battery life has been reached is a strong argument against VNS having an antiepileptogenic effect. However, as progress in the development of more relevant animal models for epilepsy has been made, the antiepileptogenic potential of neurostimulation in general is being fully explored, and some promising results have been reported, e.g. in the kindling model.38,41 In literature on
Enabling your patients to enjoy life

Just like everyone else, people with difficult-to-treat epilepsy want to enjoy their lives. However, it is extremely important to approach to patients who have tried out a number of different epilepsy treatments with little or no success.

VNS Therapy has been developed for both adults and children and is applied through a small device. This non-pharmacological treatment is an adjunctive therapy to be used with drugs, and this means that your patient’s medication intake might be reduced. In this case, we can reduce the side effects associated with the drugs they are taking.

VNS Therapy could help your patients to experience reductions in the frequency and intensity of their seizures. Furthermore, your patients may feel improvements in terms of their mood, alertness and sense of control.

In essence, the aim of VNS Therapy is to help your patients to experience increased confidence, independence and enjoyment of life.

The reality is that there are a limited number of options in dealing with difficult-to-treat epilepsy. By choosing VNS Therapy, you might well find the option that will best suit your patients.
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humans, one case report described long-lasting seizure control after explantation of the VNS device.44

The basis for the combined acute and more chronic effects of VNS most likely involves recruitment of different neuronal pathways and networks. The more chronic effects are thought to be a reflection of modulatory changes in subcortical site-specific synapses, with the potential to influence larger cortical areas. In the complex human brain these neuromodulatory processes require time to build up. Once installed, certain antiepileptic neural networks may be more easily recruited, e.g. by changing stimulation parameters that may then be titrated to the individual need of the patient. This raises hope for potential antiepileptogenic properties of VNS using long-term optimised stimulation parameters that may affect and potentially reverse pathological processes that have been installed over a long period of time. However, from a clinical point of view, as yet VNS cannot be considered a curative treatment.

Conclusion

Despite the fact that VNS is accepted in epilepsy centres worldwide as a valuable and reliable therapeutic option for patients who are unsuitable candidates for resective surgery, some specific issues remain to counteract its full therapeutic potential. On the basis of currently available data, the responder rate in patients treated with VNS is not substantially higher compared with recently marketed antiepileptic drugs. Efforts to decrease the number of non-responders may increasingly justify implantation with a device. To increase efficacy, research towards the elucidation of the MOA is crucial. In this way, rational stimulation paradigms may be investigated.

Animal research should be directed towards the identification of a useful model to evaluate the seizure-suppressing effects of VNS. The initial experiments investigating VNS in the PTZ and maximal electroshock model prove difficult to be reproduced even in the hands of experienced researchers. At Ghent University Hospital, VNS has shown efficacy in the motor stimulation model.43 The seizure threshold in this animal model significantly increases following one hour of VNS. This model can now be applied to investigate the efficacy of different stimulation parameters. Apart from the acute seizure-suppressing effects of VNS, the more chronic and estimated neuromodulatory effects should be further investigated in the laboratory. Investigating VNS in a chronic setting requires efforts to investigate animals in chronic conditions with specifically designed electrodes that allow long-term treatment. At Ghent University Hospital, a chronic video-EEG monitoring unit with customised miniature vagus nerve electrodes has been designed for this purpose. Ongoing research is investigating the long-term effects of VNS in the rapid kindling model. The ultimate goal may be to investigate the efficacy of VNS in spontaneous seizures, as observed in status epilepticus models. Indications of involvement of specific neurotransmitters in VNS have been established. Further investigation of this topic may be performed using microdialysis techniques in different animal models.

Because of the variability of different phenotypes of epilepsy, it seems simplistic to assume that there are specific combinations of stimulation parameters that will optimally benefit different types of epilepsy and all refractory individuals. Individually guided stimulation parameter titration may be a more successful avenue to follow. Research should therefore be directed towards finding non-invasive measures that can guide individual titration. Neurophysiological investigation, such as evoked potentials and EEG recording in particular, is encouraging.

Interesting research lines include the investigation of VNS efficacy in specific epilepsy conditions and in other neurological conditions. Case reports on the efficacy of VNS in status epilepticus are positive and require further prospective studies in larger patient groups.

From a more experimental view, VNS may be considered part of a closed-loop system whereby triggered VNS is performed on a more individualised basis. Research towards the development of transcutaneous systems may allow predictive factors to be identified for response before chronic implantation is performed.

With a rapidly evolving biomedical world, various neurostimulation modalities will be applied in patients with refractory epilepsy. Future studies will have to show the precise position of VNS in comparison with treatment such as deep brain stimulation and transcranial magnetic stimulation.