FACULTY OF MEDICINE AND HEALTH SCIENCES

Exploring the Therapeutic Potential of Vagus Nerve Stimulation in Multiple Sclerosis: Insights from Preclinical Models

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GHENT UNIVERSITY

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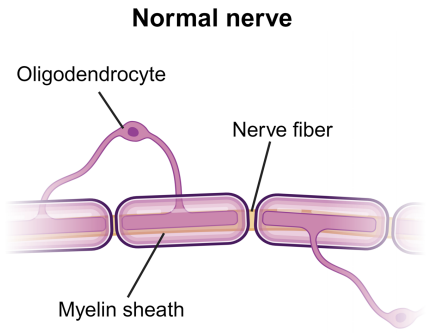
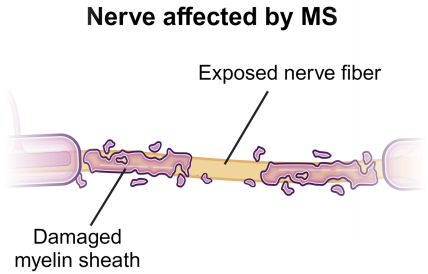
4BRAIN

Introduction

Multiple Sclerosis

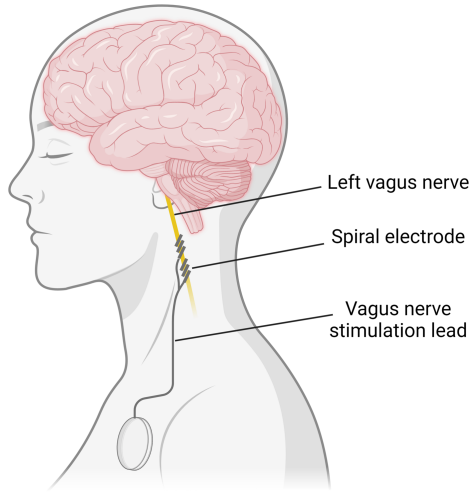
Multiple sclerosis (MS) is a chronic neurological disease marked by autoimmune myelin loss (demyelination) of the central nervous system (CNS), causing various symptoms such as imbalance, reduced strength, vision disturbances, and cognitive dysfunction. MS affects about 2.8 million people worldwide, mostly under the age of 30, making it the leading cause of non-traumatic disability in this age group. The primary treatment involves disease-modifying therapies (DMTs) that reduce relapses and prevent disability but do not halt long-term disease progression and carry risks like serious infections and high costs.





Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) presents a promising treatment, being more cost-effective and safer, with anti-inflammatory effects and potential to improve myelin repair. Recent animal studies showed that VNS can reduce inflammation in autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease, which could address the therapeutic needs in MS.



Research aims

The aim of this PhD dissertation is to investigate the treatment potential of VNS in an animal model of MS, focusing on its effects on inflammation by microglia and astrocytes, the main immune cells of the CNS, and on myelin repair of a demyelinating lesion. First, VNS was tested in the lysolecithin model, in which myelin loss and inflammation is induced by injecting a toxic substance in the rat brains (Study 1). Next, the use of laryngeal muscle evoked potentials (LMEPs) to verify correct VNS implantation and function was investigated, aiming to improve VNS research

in rodents (Study 2). Lastly, an experiment was performed to develop an adaptation of the classical experimental autoimmune encephalomyelitis (EAE) model, often used in MS research, aiming to develop a typical MS lesion in a localized and preclinical manner.

Research

Study 1: Effect of VNS on demyelination, remyelination and neuroinflammation in rats

Study 1 explored the effect of VNS on demyelination and inflammation in a rodent MS model. Lewis rats were injected with lysolecithin into their corpus callosum, inducing localized myelin loss and inflammation. Next, they were treated with VNS, using either continuous VNS (cVNS) or one minute VNS daily, or with control treatment (no stimulation). Results showed that cVNS significantly reduced inflammation and improved remyelination in the brain compared to controls. Specifically, cVNS increased the repair of damaged myelin sheaths (remyelination) by 57.4%, while reducing the activation of immune cells in the lesion. The results suggest that VNS could promote remyelination by modulating immune cell activity and enhancing nerve cell connections. Future studies should further explore the therapeutic potential of VNS in other MS models.

Study 2: Use of LMEPs in rodent VNS research

Study 2 examined the use of LMEPs as a marker for proper nerve-electrode contact during VNS experiments in rats. Female Lewis rats were implanted with custom-made VNS electrodes. After recovery, minimally invasive LMEP recordings were performed twice, with inversing electrode polarity, to assess the VNS-induced laryngeal muscle responses. LMEP responses were detected in 80.4% of the animals, with specific measurements of latency and stimulation threshold noted. The study confirmed that minimally invasive LMEP recording is a reliable method to verify the effectiveness of the nerve-electrode interface during VNS experiments in rodents.

Study 3: Development of a focal EAE model in the corpus callosum of rats

Study 3 aimed to develop a focal EAE model in the corpus callosum of Lewis rats to further investigate the immune-mediated demyelination typical for MS. Female Lewis rats were immunized against myelin protein (MOG) and three weeks later injected with vascular endothelial growth factor (VEGF) to induce localized blood-brain barrier (BBB) opening and inflammation in the corpus callosum. Immunization was successful, and after injection brain MRI showed edema and contrast enhancement of the corpus callosum. However, histology revealed only limited inflammation, not more than the control side, without significant demyelination in the targeted brain region. Further optimization of the model is needed to improve the model's effectiveness for studying MS.

General

Curriculum Vitae

Helen Bachmann obtained her Master of Medicine in 2018 with great distinction. After two years of clinical residency in Neurology, she started a PhD trajectory specializing in preclinical research with focus on MS and VNS. Besides publishing three A1 publications, she presented her work at several international congresses, including the European Academy of Neurology and the Congress of the European Committee for Treatment and Research in Multiple Sclerosis.

CONCLUSION

This dissertation investigates the potential of VNS as a treatment for MS, with a focus on its impact on inflammation and myelin repair in animal models. The findings demonstrate that VNS significantly reduces brain inflammation and enhances remyelination in rats, while LMEPs offer a reliable, minimally invasive method to assess nerve-electrode function. Further research is necessary to optimize the focal EAE model in the corpus callosum of rats and to explore the full therapeutic potential of VNS in treating MS.

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