FACULTY OF MEDICINE AND HEALTH SCIENCES

Exploration of the effects of vagus nerve stimulation on tumor growth in a preclinical model for glioma-related epilepsy and identification of a marker for effective stimulation

Charlotte Bouckaert

Thesis submitted to fulfill the requirements for the degree of Doctor in Health Sciences ~2021~

GHENT UNIVERSITY

Summary of the research

Epilepsy is a chronic brain disorder characterized by recurrent spontaneous seizures consisting of a sudden change in behavior and/or consciousness. Approximately 50 million people worldwide suffer from this disease, and one third of the patients do not benefit from treatment with antiepileptic drugs (AEDs).

In these patients, electrical stimulation of the tenth cranial nerve or vagus nerve - i.e., **vagus nerve stimulation (VNS)** - is often considered. Despite being effective in two-thirds of patients, optimal stimulation parameters are not known for this safe and minimally invasive treatment and one third of the patients remain non-responders to this therapy.

Glioblastoma (GB) is the most common and aggressive malignant brain tumor in adults. The current standard of care consists of maximum safe surgical resection, followed by radiation and chemotherapy. Despite aggressive treatment, GB remains an incurable disease with a median survival of less than two years. Epileptic seizures are common in GB patients and one third of seizures persist after AED treatment. Better treatments targeting both GB progression and tumor-related epilepsy are highly needed and require a well-characterized preclinical model for GB-related epilepsy.

In a first study, we investigated whether VNS-induced contraction of laryngeal muscles can be recorded non-invasively during routine hospital examinations. These **VNS-induced laryngeal muscle-evoked potential (LMEP) recordings** may provide a marker to assess effective vagal nerve fiber activation and may be useful to guide individual titration of stimulation parameters.

As well-characterized preclinical models for GB-related epilepsy were lacking and are important to investigate treatments targeting both GB progression and related epilepsy, we focused on the development of **a rat model for glioma-related epilepsy** in a second study.

In a third study, we further characterized the developed rat model using **magnetic resonance imaging (MRI)** and immunohistochemical analyses.

VNS is already used to treat drug-resistant seizures in brain tumor patients and has a similar efficacy as in epilepsy patients without brain tumors. However, the effect of VNS on brain tumor progression has never been investigated. It is important to know **the influence of VNS on brain tumor progression,** which was explored in a fourth study.

Most electrodes used for electroencephalography recordings (EEG) or stimulation are incompatible with MRI, due to the high field strengths of scanners required in preclinical research with small animals. In a final study, we tested **different MRI-compatible EEG and VNS electrodes** to be used for chronic in vivo studies.

Publications

Development of a rat model for glioma-related epilepsy. Bouckaert C *et al*. International Journal of Molecular Sciences (2020).

Comparison of in vivo and ex vivo magnetic resonance imaging in a rat model for glioblastoma-associated epilepsy. Bouckaert C *et al*. Diagnostics (2021).

Laryngeal muscle-evoked potential recording as an indicator of vagal nerve fiber activation. Bouckaert C *et al*. Submitted (2021).

Public defense

The public defense will be held on campus.
Venue: Het Pand (Onderbergen 1, 9000 Gent – room Rector Vermeylen)
Date and Time: October 22, 2021 – 5 PM

Short Curriculum Vitae

Charlotte Bouckaert (° January 3, 1995) graduated at Ghent University in 2017 as Master of Science in Biomedical Sciences (major Neuroscience) and received an award for "best student Biomedical Sciences over whole academic career" by Fujirebio Europe. She was also selected to participate in the *Honours programme in Life Sciences: breaking frontiers*. This was a two-year program comprising a general part involving compulsory lessons and a more specific part involving active participation in a research project, in her case about the role of the noradrenergic system in the mechanism of action of vagus nerve stimulation. Certification was achieved after presenting the work in poster format and contributing to one peer-reviewed publication: '**The antidepressant-like effect of vagus nerve stimulation is mediated through the locus coeruleus.** Grimonprez A *et al*. Journal of Psychiatric Research (2015)'. In 2017, she started working as a PhD researcher at the Faculty of Medicine and Health Sciences in the 4BRAIN lab at Ghent University, supported by a junior researcher ('Aspirant') grant from FWO. During her PhD, she focused on the development and characterization of a rat model for glioma-related epilepsy. Moreover, she investigated a possible non-invasive marker for effective activation of the vagus nerve in epilepsy patients treated with vagus nerve stimulation and explored the effects of this treatment on glioblastoma progression and related seizures in the developed rat model. She followed several courses of the Doctoral Training Program at Ghent University and supervised three master thesis projects. She presented her research at multiple (inter)national conferences. The PhD trajectory resulted in two first-authored and six co-authored peer-reviewed publications. Moreover, she is first author of one submitted manuscript.

Supervisors

Prof. dr. Robrecht Raedt
Supervisor
Department of Head and Skin
Ghent University, Belgium

Prof. dr. Kristl Vonck
Co-supervisor
Department of Head and Skin
Ghent University, Belgium

Examination Committee

Prof. dr. Jolanda van Hengel
Chair
Department of Human Structure and Repair
Ghent University, Belgium

dr. Lars Emil Larsen
Secretary
Department of Head and Skin
Ghent University, Belgium

Prof. dr. Guy Laureys
Department of Head and Skin
Ghent University, Belgium

Prof. dr. Tom Boterberg
Department of Human Structure and Repair
Ghent University Hospital, Belgium

Prof. dr. Ilse Smolders
Department of Pharmaceutical Sciences
Vrije Universiteit Brussel, Belgium

Prof. dr. Arthur Cukiert
Department of Neurosurgery
São Paulo Epilepsy Clinic, Brazil

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CONTACT
Charlotte Bouckaert
charlotte.bouckaert@ugent.be

Supervisor
Robrecht Raedt
robrecht.raedt@ugent.be

Department of Head and Skin
4BRAIN
T +32 9 332 33 55

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https://biblio.ugent.be/person/802002661472

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