

The neuromodulatory effect, safety and effectiveness of Vagus Nerve Stimulation

Akademisk avhandling

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av

David Révész

Fakultetsopponent:

Professor Paul Boon

Department of Internal medicine, Ghent University, Belgium

Avhandlingen baseras på följande delarbeten

- I. Révész D, Tjernstrom M, Ben-Menachem E, Thorlin T. Effects of vagus nerve stimulation on rat hippocampal progenitor proliferation. *Experimental Neurology*. 2008 Dec;214(2):259-65.
- II. Johannessen H, Révész D, Kodama Y, Cassie N, Skibicka KP, Barrett P, Dickson S, Holst J, Rehfeld J, van der Plasse G, Adan R, Kulseng B, Ben-Menachem E, Zhao CM, Chen D. Vagal Blocking for Obesity Control: a Possible Mechanism-Of-Action. *Obesity Surgery*. 2017 Jan;27(1):177-185.
- III. Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. *Journal of Neurosurgery Pediatrics*. 2016 Jul;18(1):97-104.
- IV. Révész D, Rydenhag B, Ben-Menachem E. Estimating long-term VNS efficacy: Accounting for AED regimen changes. *Submitted*

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ABSTRACT

Background: Vagus nerve stimulation (VNS) is an adjunctive palliative neuromodulatory treatment for drug resistant epilepsy (DRE) and chronic depression. It has also been proposed as a treatment for many other conditions such as chronic pain, heart failure, and Alzheimer's disease. Vagal Blocking Therapy (VBLOC) was recently approved for the treatment of obesity. However, the mechanisms of action still remains unclear and its long-term safety and efficacy in combination with antiepileptic drugs (AEDs) needs to be further evaluated. The aim of this thesis was to study the action of VNS on hippocampal neurogenesis as a possible mechanism of action on depression, to evaluate VBLOC as a new treatment model for obesity, and to study the long-term safety and effectiveness of VNS.

Patients and methods: In Study I rats were implanted with VNS and different stimulation parameters were compared to sham, in order to evaluate the effect of VNS on hippocampal progenitor proliferation. The number of Bromodeoxyuridine (BrdU) positive cells was compared between groups. In Study II rats were implanted with VBLOC, and leads were placed around the gastric portion of the vagus nerve. Body weight, food intake, hunger/satiety, and metabolic parameters were monitored and compared between control and sham-stimulated animals. In Study III all patients that had been implanted with VNS between 1990 and 2014 were analyzed for surgical and hardware complications. In Study IV data from 130 consecutive patients implanted with VNS between the years 2000 and 2013 was analyzed for seizure frequency and AEDs prior to VNS implantation as well as at 1, 2, and 5 years postoperatively. Study III and IV were retrospective cohort studies.

Results: VNS at the output current of 0.75 mA for 48 hours showed a significant increase in progenitor cell proliferation. VBLOC reduced food intake and body weight, and was associated with increased satiety but not with decreased hunger. Complications occurred in 8.6 % of all VNS surgeries in patients with DRE. The most common complications, all with an occurrence rate of about 2 %, were postoperative hematoma, infection, and vocal cord paralysis. Hardware related complications occurred in 3.7 % of all implanted VNS systems, and significantly less lead associated complications occurred during 2000–2014 compared to 1990–1999. There was a significant seizure reduction overall (all $p < 0.001$) regardless of AED regimen, and VNS efficacy increased with time from 22.1 % at 1 year to 43.8 % at 5 years.

Conclusions: VNS induces stem cell proliferation in the rat hippocampus, which supports the notion that hippocampal plasticity is involved in the antidepressant effect of VNS. The mechanism of action of VBLOC as a treatment for obesity could be regulated by inducing satiety through vagal signaling, leading to reduced food intake and loss of body weight. The treatment was well tolerated in rats. VNS is a safe palliative neuromodulatory treatment for DRE, and the 25 years of follow-up to study safety is of great strength considering that VNS can be a life-long treatment with repeated surgeries. VNS efficacy increased with time, with improvements seen up to 5 years, and did not differ between patients that had altered or remained on the same AEDs throughout the study period.

Keywords: Vagus nerve stimulation, VNS, Neuromodulation, Neurogenesis, VBLOC, Epilepsy, Depression, Safety, Efficacy, Effectiveness