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High-frequency burst vagal nerve simulation therapy in a natural primate model of genetic generalized epilepsy

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ABSTRACT

Purpose: Since the approval of Vagal Nerve Stimulation (VNS) Therapy for medically refractory focal epilepsies in 1997, it has been also reported to be effective for a wide range of generalized seizures types and epilepsy syndromes. Instead of conventional VNS Therapy delivered at 20–30 Hz signal frequencies, this study evaluates efficacy and tolerability of high-frequency burst VNS in a natural animal model for genetic generalized epilepsy (GGE), the epileptic baboon.

Methods: Two female baboons (B1 *P.h. Hamadryas* and B2 *P.h. Anubis x Cynocephalus*) were selected because of frequently witnessed generalized tonic-clonic seizures (GTCS) for VNS implantation. High-frequency burst VNS Therapy was initiated after a 4–5 week baseline; different VNS settings (0.25, 2 or 2.5 mA, 300 Hz, 4 vs 7 pulses, 0.5–2.5 s interburst interval, and intermittent stimulation for 1–2 vs for 24 h per day) were tested over the subsequent 19 weeks, which included a 4–6 week wash-out period. GTCS frequencies were quantified for each setting, while seizure duration and postictal recovery times were compared to baseline. Scalp EEG studies were performed at almost every setting, including intermittent light stimulation (ILS) to evaluate photosensitivity. Pre-ILS ictal and interictal discharge rates, as well as ILS responses were compared between trials. The Novel Object test was used to assess potential treatment effects on behavior.

Results: High-frequency burst VNS Therapy reduced GTCS frequencies at all treatment settings in both baboons, except when output currents were reduced (0.25 mA) or intermittent stimulation was restricted (to 1–2 h/day). Seizure duration and postictal recovery times were unchanged. Scalp EEG studies did not demonstrate treatment-related decrease of ictal or interictal epileptic discharges or photosensitivity, but continuous treatment for 120–180 s during ILS appeared to reduce photoparoxysmal responses. High-frequency burst VNS Therapy was well-tolerated by both baboons, without cardiac or behavioral changes. Repetitive muscle contractions involving the neck and left shoulder girdle were observed intermittently, most commonly at 0.5 interburst intervals, but these were transient, resolving with a few cycles of stimulation and not noted in wakefulness.

Conclusions: This preclinical pilot study demonstrates efficacy and tolerability of high-frequency burst VNS Therapy in the baboon model of GGE. The muscle contractions may be due to aberrant propagation of the stimulus along the vagal nerve or to the ansa cervicalis, but can be reduced by minimal adjustment of current output or stimulus duration.

1. Introduction

Vagal Nerve Stimulation (VNS) Therapy provides an effective treatment for medically refractory focal epilepsies. Initially, the therapeutic effects of VNS were mediated by chronic intermittent stimulation as well as the ability to prevent or abort seizures by activating the device with a handheld magnet (Ben-Menachem, 2001; Morris and Mueller, 1999). The most recent model, the AspireSR® (Model 106), also provides stimulation in response to heart rate changes that may be associated with focal seizures (Boon et al., 2015).

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The original FDA approval for VNS Therapy hinged on the comparative efficacy between "high" (30 Hz frequency, pulse duration 500 microseconds, 5 min intervals, magnet activation available) vs "low" (1 Hz, pulse duration 130 microseconds, 3 h intervals, magnet activation not available) stimulation groups (Handforth et al., 1998). In the initial studies, a greater than 50% seizure reduction was experienced by 23–43% patients, with the responder rates increasing over the course of 3 years (Ben-Menachem, 2001; Morris and Mueller, 1999). In the meantime, Cyberonics (Houston, Texas, a fully owned subsidiary of LivaNova US Inc.) developed a new treatment paradigm utilizing high-frequency burst stimulation at 100–350 Hz, instead of the currently approved 20–30 Hz, in order to improve tolerability and efficacy. High-frequency burst stimulation refers to 4–7 pulses of high-frequency stimulation, each pulse lasting 250 μs with interburst intervals of 0.5–2.5 s. Initial tests of high-frequency burst stimulation in rodent and nonhuman primates models showed efficacy and tolerability (Alexander and McNamara, 2012; Ito and Craig, 2005). The rationale for adjusting the number of pulses per burst and varying the interburst intervals is to optimize the post-synaptic potentials of thalamic neurons. Paired-pulse stimulation of the vagus nerve potentiated post-synaptic potentials in the parafascicular nucleus of the thalamus compared to single pulse stimulation (Ito and Craig, 2005; Ito and Craig, 2008).

Over fifty years ago, nonhuman primates provided an important resource for the development and testing of antiepileptic medications and neurostimulation (Naquet and Meldrum, 1972; Hemmy et al., 1977; Killam, 1979; Lockard et al., 1990). One of the most studied models, the baboon, exhibits natural, genetic generalized epilepsy (GGE) with photosensitivity (Naquet and Meldrum, 1972; Killam 1979). The modulation of photoconvulsive responses was utilized for testing medication effects in the epileptic baboon. Experimental nonhuman primate models, such as the alumina-gel model of focal epilepsy in the macaque, also played a significant role in the development of VNS Therapy (Lockard et al., 1990). The main advantages of nonhuman primate models include the neuroanatomic similarities to humans for better understanding of the electrophysiological effects and tolerability of VNS Therapy.

While there are several studies reporting efficacy of VNS in idiopathic or genetic generalized epilepsies, most of them are retrospective (Ng and Devinsky, 2004; Holmes et al., 2004; Kostov et al., 2007). This study, utilizing a well-documented model of GGE in the baboon, which closely corresponds to human idiopathic generalized epilepsies, represents an attempt to demonstrate efficacy and tolerability of high-frequency burst VNS Therapy over a five-month period. Primary treatment outcomes included change in generalized tonic-clonic seizures (GTCS) across the different treatment settings, measured as a weekly seizure average, while secondary outcomes included ictal or interictal changes on scalp EEG, including photosensitivity, as well as behavioral effects of VNS Therapy.

2. Materials & methods

2.1. Animal selection

Two baboons were selected on the basis of their baseline frequency of generalized tonic-clinic seizures (GTCS). One 16 year-old female baboon (B1; *P.h. Hamadryas*) had seizures mainly upon awakening, which increased during the course of her pregnancy and peripartum period. She was witnessed to have had 15 GTCS over a two-year period. The second 10 year-old female baboon (B2; *P.h. Anubis x Cynocephalus*) was noted to have GTCS in each of six sedations using ketamine within the preceding three years, and evidence of chronic periorbital scarring, which can be a marker for epilepsy (Szabó et al., 2014). Otherwise, both baboons were neurologically intact and otherwise healthy. The baboons underwent baseline scalp EEG studies and MRI scans of the brain (R21 N084198). Scalp EEG studies were repeated 4 times in B1 and 8 times in B2 (2 of which were excluded due to technical difficulties

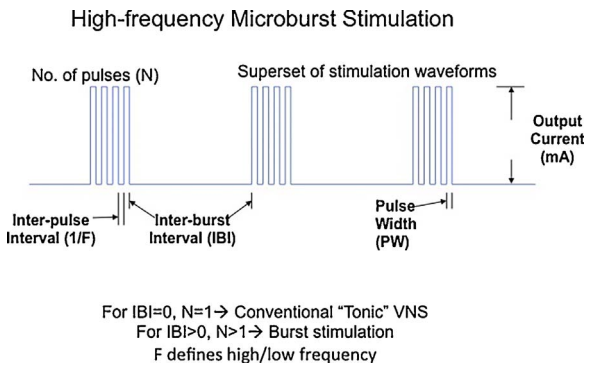

Fig. 1. High-Frequency Burst Stimulation Paradigm.

or alternate sedation), all confirming the diagnosis of GGE with or without photosensitivity. The brain MRI scan of B1 was normal, but B2 had an enlarged left occipital horn, or colpocephaly, which is also highly correlated with craniofacial trauma, and hence is likely to be the result of, and not the cause for, seizures (Szabó et al., 2016). All experiments complied with the ARRIVE guidelines (http//:www.nc3rs.org.uk). These studies were approved by the Institutional Animal Care and Use Committee of the Texas Biomedical Research Institute. The baboons were treated in strict accordance with the United States Public Health Service's *Guide for the Care and Use of Laboratory Animals* (Institute for Laboratory Research, 2011) and the *Animal Welfare Act* (Animal Welfare Act, 2008).

2.2. VNS implantation

Both animals were implanted with a VNS Therapy System® (Cyberonics, Houston, TX), consisting of a pulse generator (Demipulse™Model 103) and a lead with helical electrodes (single-pin bipolar lead, 3.0 mm size). The research versions of Model 103 VNS devices are capable of delivering high-frequency burst stimulation (Fig. 1). Under general anesthesia, the vagal nerve was dissected out of the vagosympathetic trunk (lies laterally to sympathetic portion) and the lead was coiled around it. The generators were placed interscapularly, both to keep the device out of reach and to avoid injury to the air sacs. During the surgery, the end tidal CO_2, inspiratory oxygen saturation and peripheral hemoglobin concentration were monitored continuously. After checking the impedance, high-frequency (300 Hz) burst VNS Therapy was delivered in the operating room with ECG monitoring at current outputs beginning at 0.25 mA, and gradually increased to 2.5 mA, with no observed alteration of heart rate. No heart rate changes were noted. Both baboons received buprenorphine 0.01 mg/kg for up to 48 h postoperatively. The device was turned on in B1 at the time of surgery, while in B2 the device was only turned on 4 weeks after the surgery, again after titrating the current output to 2.5 mA while sedated with ketamine, in both cases closely monitoring the heart rate.

2.3. Study design

The baboons were housed in single cages, which were placed side-by-side. Lights were turned on and off 12 h at a time (usually 7 am and 7 pm), but often turned on briefly between midnight and 1 am for a few minutes, while veterinary technicians were checking on the animals. An Axis (Lund, Sweden) camera with infrared capabilities for night-time recordings, was set up with a frontal view to one or both cages from a three-meter distance. B1 was monitored for 24 weeks (including a five-week baseline, and a four-week pause), whereas B2 was monitored for 23 weeks (including a four-week baseline, and a six-week pause).

The overall strategy for adjusting VNS settings, was first to change interstimulus intervals, thereafter adjusting the number of pulses per