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Hypothesis

Can natural ways to stimulate the vagus nerve improve seizure control?

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ABSTRACT

The vagus nerve (VN) is the longest cranial nerve, innervating the neck, thorax and abdomen, with afferent fibers transmitting a range of interoceptive stimuli and efferent fibres to somatic structures and autonomic preganglions. Over the last few decades, electrical stimulation of the VN using implanted devices (VNS) has been developed leading to its approval for the treatment of epilepsy and depression. More recently, non-invasive devices to stimulation the VN have been developed. The VN has many functions and the activity that is most amenable to assessment is its effect in controlling the cardiac rhythm. This can be easily assessed by measuring heart rate variability (HRV). Decreased HRV is a result of poorer vagal parasympathetic tone and is associated with a wide range of ill health conditions including a higher risk of early mortality. People with epilepsy, particularly those with poorly controlled seizures, have been shown to have impaired parasympathetic tone. So, might natural ways to stimulate the VN, shown to improve parasympathetic tone as indicated by increased HRV, improve seizure control? There are numerous natural ways that have been shown to stimulate the VN, improving HRV and hence parasympathetic tone. These natural ways fall mainly into 3 categories – stress reduction, exercise, and nutrition. Though the natural ways to stimulate the VN have been shown to increase HRV, they have not been shown to reduce seizures. The exception is listening to Mozart's music, which has been shown to increase parasympathetic tone and decrease seizures. Clearly much more work is required to examine the effect of the various ways to increase HRV on seizure occurrence.

1. Introduction

The vagus nerve (VN), the 10th cranial nerve, is the longest cranial nerve, originating from the medulla oblongata and exiting the skull through the jugular foramen, innervating the structures in the neck, thorax, and abdomen. It is involved in autonomic, cardiovascular, respiratory, gastrointestinal, immune, and endocrine systems. The vagal afferents sense a variety of interoceptive stimuli including pressure, pain, stretch, temperature, chemical, osmotic pressure, and inflammation. The vagal efferents innervate both somatic structures and the autonomic nervous system, with fibers to both sympathetic and parasympathetic preganglions. Most VN fibers (60–80%) are afferent fibres from the visceral organs. Detailed anatomy and physiology of the VN have been reviewed [1].

Electrical VN stimulation (VNS) was first tested during the late 19th century, by James Corning, an American neurologist. He was not able to demonstrate an effect on seizures. Corning hypothesized that the VNS would affect cerebral blood flow, which was thought at that time to be the cause of epilepsy. By 1952, VNS was shown in animals to affect the electric currents in the VN and produce changes in the ECG [2]. Subsequent animal studies (reviewed in [3]) contributed to better understanding of VNS and these led to human studies [4,5]. In 1994, a randomized, multicenter, double-blind study in 67 people with refractory seizures showed a significant reduction in seizure frequency after 14 weeks of VNS [6]. In 1997, the US Food and Drug administration approved an implanted left cervical VNS device for managing treatment-refractory epilepsy, and subsequently, in 2005, approved its use for chronic treatment-resistant depression. A VNS device has also received in 2015 European approval for the treatment of chronic heart failure. This approval was based on an open study in 60 people with severe heart failure, showing significant improvement in a number of cardiac function measures [7].

More recently, non-invasive VNS devices have also been developed. A trans-auricular VNS device, one such non-invasive device, which stimulates the auricular branch of the VN, was approved in Europe for the treatment of epilepsy and depression in 2010 [8], and pain in 2012 [9]. A non-invasive hand-held trans-cervical VNS device, which stimulates the cervical branch of the VN, has received European clearance for use in a range of conditions including acute and prophylactic treatment of primary headaches, medication overuse headache, reactive airway

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disease, as well as adjunctive therapy for epilepsy, and for preventing and reducing the symptoms of certain anxiety and depression conditions, gastric mobility disorders, and irritable bowel syndrome [3].

2. VNS mechanism

The precise mechanism of action of VNS is not fully understood. It has many effects, which can by itself but more likely in concert with others exert the observed anti-seizure properties. These effects include desynchronization of neuronal activity, hippocampal plasticity, anti-inflammation, and modulation of neurotransmitter release [10].

The VN senses peripheral inflammation and the signals transmitted to the brainstem then, in turn, generate action potentials carried by the efferent fibers of the VN to the spleen where the production of pro-inflammatory cytokines are inhibited. This has been termed the inflammatory reflex [11]. VNS can activate this reflex. Using the endotoxemic rat model, an anti-inflammatory effect was elicited by trans-auricular stimulation of the auricular branch of the VN. The study showed trans-auricular stimulation decreased levels of inflammatory cytokines in serum, such as TNF-α, IL-1β, and IL-6, as well as the pro-inflammatory transcription factor NF-κB. These anti-inflammatory effects were abolished by vagotomy or administration of an α7nAChR (nicotinic acetylcholine receptor) antagonist [12]. Indeed, a number of studies using animal models of inflammatory diseases have demonstrated the beneficial effects of VNS [13].

Therefore, VNS probably exerts its anti-seizure effects through a combination of a number of central nervous system effects and its peripheral anti-inflammatory effects.

VNS can trigger the systemic release of catecholamines that can alleviate asthma attacks. It induces anti-nociception by modulating multiple pain-associated structures in the brain and spinal cord affecting peripheral/central nociception, opioid response, inflammation process, and pain-related behavior [10]. VNS is currently undergoing many trials to explore its potential for various other clinical disorders: headache, arthritis, asthma, pain, fibromyalgia, bipolar disorder, and dementia [1].

3. Assessing vagus nerve function

The VN is complex with afferents sensing a variety of interoceptive stimuli, and efferents to the autonomic nervous system and somatic structures including the majority of the muscles to the pharynx and larynx. Although the VN serves many functions, its role in generating parasympathetic tone is central to our discussion. The vagal parasympathetic tone is modulated by excitatory input from baroreceptors, chemoreceptors, trigeminal receptors, and cardiopulmonary receptors; and inhibitory input from pulmonary stretch receptors, visceral and somatic receptors [14]. Vagal activity can be assessed by examining its effects on the heart using various procedures.

3.1. Autonomic function tests

Tests to assess the autonomic effects of VNS include deep breathing, Valsalva maneuver, isometric exercise, cold pressor, and tilt-table test. Heart rate and blood pressure changes during the tests provide a measure of sympathetic and parasympathetic reactivity [15]. These tests are used less often and have been largely replaced by measures of heart rate variability (Heart rate variability).

3.2. HRV using electrocardiogram (ECG)

Successive R-R intervals are obtained from continuous ECG recordings. These provide instantaneous heart rates which are used to calculate HRV. Heart rate variability depends mainly on the influence of sympathetic and vagal activity on the sinus node. There are many ways to analyze ECG recordings for HRV. Though there is some consensus on the interpretation of the results, there are still areas of debate. The two main methods most commonly used are assessing time domain parameters and assessing frequency domain parameters. In the time domain analysis, HRV is generally assessed by determining SDNN (SD of R–R intervals); however, other measures can also be used including SDANN (SD of average R–R intervals), RMSSD (root mean square of successive differences), and the HRV triangular index [16]. In frequency domain analysis, most investigations suggest that high-frequency (HF) components reflect the parasympathetic tone, whereas low-frequency (LF) components are considered to have both sympathetic and parasympathetic influences, and LF/HF ratios are thought to reflect sympathovagal balance or sympathetic modulations [16].

In a study analyzing 24-hour ECG recordings from children, all time domain and frequency domain measures significantly correlated with each other [17]. There were, however, differences in the strength of the correlations. All time domain measures were more highly correlated with HF components than with LF components [17], which suggests that an increase in HRV (as assessed by time domain measures) generally implies a greater increase in HF components and, hence, parasympathetic tone than sympathetic tone. Hence, the following HRV parameters are generally considered to be markers of autonomic function and in particular the tone of the parasympathetic system: SDNN, RMSSD, total power, and HF power.

3.3. Heart rate variability using photoplethysmography (PPG) technology

Photoplethysmography uses an optical sensor attached to the earlobe or finger to detect cardiac pulse wave by detecting the changes to light absorption as a consequence of the changes in a number of hemoglobin molecules in the skin during the pulse wave. Heart rate variability obtained from PPG has been shown to be highly correlated with ECG-derived HRV and can be used to assess vagal tone [18]. There are a number of devices using PPG technology that are available to the public e.g. HeartMath's emWave2 for use with home computers and Inner Balance for use with Apple Inc. devices. Recently PPG technology has been implemented in mobile devices by using the cameras as the optical sensor, making home monitoring of vagal tone very easy and affordable. Also, it has been shown that the maximum variation in heart rate (the largest respiratory sinus arrhythmia, also a measure of HRV) during a 1-min deep breathing test showed a better correlation with age when compared using parameters derived from 5-min HRV recordings [18]. Hence a fairly easy algorithm can be used to determine age-adjusted vagal tone.

In general, a high HRV indicates a dominance of the parasympathetic nervous system/vagal tone, the portion of the autonomic nervous system that promotes relaxation, digestion, sleep, and recovery. The parasympathetic system is also known as the “feed and breed” or “rest and digest” system. A low HRV indicates the dominance of the sympathetic nervous system, the fight or flight component of the autonomic nervous system associated with stress, overtraining, and inflammation.

4. Decreased parasympathetic tone in people with epilepsy

In a meta-analysis including 39 studies, people with epilepsy had significantly lower HF, SDNN, and RMSSD compared to controls. This supports the suggestion that epilepsy is associated with sympathovagal imbalance, with a decrease in parasympathetic tone [19]. In a study which evaluated 19 subjects with refractory epilepsy, RMSSD was used as the measure for HRV. Then, RMSSD was correlated with SUDEP-7 inventory, which is a measure that reflects the severity of epilepsy – the number of seizures, the duration of epilepsy, and the number of AEDs used. The study found a significant inverse correlation between RMSSD and SUDEP-7 scores, suggesting that more severe epilepsy is associated with poorer parasympathetic autonomic function [20]. In another study of 61 subjects, those with intractable epilepsy had greater sympathetic and lower parasympathetic tone compared to those with well-controlled epilepsy [15]. Hence, there is good evidence