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Review

Vagal nerve stimulation as a promising tool in the improvement of cognitive disorders

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Abstract

Vagal nerve stimulation (VNS) is known as an effective method of treatment in a number of neurological disorders. The low risk of side effects also makes it useful in clinical trials in other diseases. Branches of the vagal nerve innervate the anatomical structures known to be involved in memory processing. That is why it seems justified that several studies emphasize the impact of VNS on the cognitive and memory function in both healthy volunteers and patients with epilepsy and Alzheimer's disease. Results have shown that VNS can modulate different types of memory depending the protocol of stimulation in non-demented patients after both short term and chronic VNS application. Transcutaneous vagal nerve stimulation (tVNS), which is a non-invasive method of VNS, opens up new perspectives for different clinical applications.

Introduction

Bailey and Bremer (1938) were probably the first researchers to demonstrate that vagal nerve stimulation (VNS) caused changes to EEG. Later, Dell and Olson (1951) showed that stimulation of the cervical vagal nerve in cats evoked responses in the ventroposterior complex and intralaminar regions of the thalamus. In Zabara (1985), reported that VNS produced inhibition of seizures in dogs. Ever since, vagal nerve stimulation has been used for the benefit of patients with a variety of clinical disorders. Vagal nerve stimulation has more than three decades of clinical practice, and hundred thousand patients have been given this treatment for various neurological disorders (Ben Menachem, 2002; Sjögren et al., 2002; Hord et al., 2003; Krahl et al., 2004; Smith et al., 2005; Bonaz et al., 2013; Manta et al., 2013; Howland, 2014; Smucny et al., 2015; Straube et al., 2015; Xiang et al., 2015). Such extensive experience has opened up many opportunities to test VNS in new clinical applications. One of the most intriguing potential direction of VNS is the treatment of cognitive disorders. For the purpose of this review, we searched PubMed service for clinical and animal studies in English with the search terms "*VNS + memory*", "*memory loss + VNS*", "*cognitive impairment + VNS*", "*dementia + VNS*", and "*Alzheimer's disease + VNS*". The intention of the authors is to present the scientific background based on specific clinical applications and to attempt to analyze any differences in the obtained results. Potential clinical success in the field of memory deterioration treatment may lead to the development of technology focused on dementive disorders, including Alzheimer disease (AD).

The history of VNS goes back to the XIX century, when James Corning analyzed the anti-seizure effect from the manual suppression of the vagal nerve in epileptic patients (Lanska, 2002). After decades of animal and human trials, VNS was approved by the European Commission and the Food and Drug Administration (FDA) in the USA for treatment of drug resistant epilepsy in the late 90's. By 2019, vagal nerve stimulation was a clinically approved method for the treatment of epilepsy and depression (Clark et al., 1999; Sackeim et al., 2001; Ben-Menachem, 2002; Sjögren et al., 2002; Stefan et al., 2012). In daily clinical practice two different ways of stimulation are in use:

1 invasive vagal nerve stimulation (iVNS), through a pulse generator implanted under the skin in the upper chest and the cuff electrodes attached to the left vagal nerve (Clark et al., 1999; Hoppe et al., 2001; Sackeim et al., 2001; Ben-Menachem, 2002; Sjögren et al., 2002; Merrill et al., 2006; Smucny et al., 2015; Carreno and Frazer, 2017; Hamilton et al., 2018);

2 non-invasive transcutaneous stimulation of the vagal nerve (tVNS), which is divided into auricular transcutaneous vagal nerve stimulation (atVNS) and cervical transcutaneous vagal nerve stimulation (ctVNS) (Kreuzer et al., 2012; Stefan et al., 2012; Hein et al., 2013; Lehtimäki et al., 2013; Straube et al., 2015; Trevizol et al., 2015; Brock et al., 2017; Genheimer et al., 2017; Burger et al., 2019; Keute et al., 2019).

The parameters of stimulation - like duty cycle, frequency or output current - are based on the patient's tolerance, the presence of sides effects and stages of specific diseases. The effectiveness of iVNS in the treatment of epilepsy has already been proved in many clinical trials (Ben-Menachem, 2002; Uthman et al., 2004; Zamponi et al., 2008; Cristancho et al., 2011; Ryvlin et al., 2018). Notwithstanding its promising clinical efficacy, the invasive technique is often associated with uncomfortable side effects - like swallowing problems, coughs, throat tingling and hoarseness - and requires a complicated surgery procedure (Ramsay et al., 1994; Ben-Menachem, 2001; Dawson et al., 2016). To avoid cardiac side effects, a cuff electrode in most cases is implanted on the left vagal nerve. This solution can be easily explained by the basic anatomy of the vagal nerve. The right branches supply the sinoatrial node of the heart, whereas the left ones supply the atrioventicular node (Ardell and Randall, 1986).

In the few last years iVNS has also been tested on several comorbid diseases: depression (Rush et al., 2000; Sackeim et al., 2001; Krahl et al., 2004; George et al., 2005; Nahas et al., 2005; Dunner et al., 2006; Bajbouj et al., 2010; Aaronson et al., 2013), migraine (Hord et al., 2003; Mauskop, 2005; Lendvai et al., 2018; Tassorelli et al., 2018; Vecchio et al., 2018; Viganò et al., 2019), rheumatoid arthritis (Bonaz et al., 2013; Koopman et al., 2017), schizophrenia (Smucny et al., 2015; Osoegawa et al., 2018), inflammatory bowel disease (Bonaz et al., 2016), anxiety disorders (George et al., 2003; Howland et al., 2011), tinnitus (Suk et al., 2018; Yakunina et al., 2018) and Alzheimer disease (Sjögren et al., 2002; Merrill et al., 2006).

Surgical complications and the undesired side effects of invasive VNS has led researchers to a new, completely non-invasive way of stimulation. tVNS entered clinical treatment in 1997, receiving FDA and certification mark clearance. Its clinical effectiveness and its physiological action are similar but with fewer side effects and greater tolerability reported by patients using tVNS (Redgrave et al., 2018).

Section snippets

Anatomy and physiology of the vagal nerve - connections with the brain areas involved in memory processes

The vagal nerve (VN), as the longest cranial nerve and being a crucial part of the autonomic nervous system, exerts a wide range of effects on the body (Howland, 2014). It is particularly involved in the maintenance of homeostasis by controlling the immune system, motor functions, glandular secretions, digestion, respiration and heart rate (Berthoud, 2008; de Lartigue, 2016; Yuan and Silberstein, 2016; Breit et al., 2018). The vagal nerve is a mixed nerve made up of 80 % sensory (afferent)…

Alzheimer’s disease as an example of memory impairment

Alzheimer’s disease is the most prominent examples of memory and cognitive disorders which lead to neurons death and, in consequence, to significant intellectual deficit. It has been one of the biggest challenges in the field of neurology and neurophysiology over the past 50 years (Blessed et al., 1968; Folstein et al., 1975; Mahandra, 1984; Cummings and Benson, 1992). This problem has grown substantially due to the aging population and age-related, dementia-producing neurodegenerative diseases …

Vagal nerve stimulation and cognition

Evidence coming from human and animal trials has revealed a new, potential, clinical applications of VNS (Ben-Menachem, 2002; Sjögren et al., 2002; Hord et al., 2003; Krahl et al., 2004; Bonaz et al., 2013). Experiments conducted by Clark et al. (1995, 1998) show that iVNS may impact memory consolidation and performance. Specifically, those authors concluded that stimulation of vagal afferent fibers can modulate memory storage and has a memory-enhancing effect.

A possible mechanism of VNS…

Vagal nerve stimulation in clinical cognitive studies

The latest clinical trials have engaged both iVNS and tVNS in new applications. However, the authors used various parameters of stimulations and evaluated different cognitive results.…

Conclusions

Almost 30 years of therapeutic experience in the field of therapeutically-effected VNS has not provided a comprehensive answer concerning the mechanism underlying its clinical effectiveness. However, its clinical effectiveness *per se* has never been questioned. It is promising that technological progress has recently brought to medical practices a non-invasive method of VNS which opens up brand-new possibilities in clinical trials. The clinical trials performed to date have applied different…

Declaration of Competing Interest

There are no conflicts of interest.…

Acknowledgements

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Transcutaneous vagus nerve stimulation boosts associative memory in older individuals

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Epilepsy Behav. (2001)

C. Helmstaedter *et al.*

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Epilepsy Res. (2001)

C.L. Harden *et al.*

A pilot study of mood in epilepsy patients treated with vagus nerve stimulation

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Core candidate neurochemical and imaging biomarkers of Alzheimer's disease

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P. Hamilton *et al.*

Clinical outcomes of VNS therapy with AspireSR® (including cardiac-based seizures detection) at a large complex epilepsy and surgery centre

Seizure (2018)

S.C. Guy *et al.*

The role of overt rehearsal in enhanced conscious memory for emotional events

Conscious. Cogn. (1999)

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> …Thus, direct stimulation of VN afferent fibers in the ear may produce an effect similar to the effect of classic VNS in reducing depression symptoms. This possibility has led to the development of transcutaneous auricular VNS (taVNS),15–21 a noninvasive, low-cost, and well-tolerated alternative to VNS that can be self-administered.22,23 Recently, taVNS has been used to treat depression22,24–31 and has achieved some promising results.…

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2022, Neuromodulation

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>
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