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Advances of Research on Auricular Vagus Nerve Stimulation for Treatment of Nervous System Diseases

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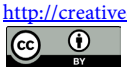

Abstract

As a new type of nerve regulation technology, Vagus Nerve Stimulation is currently used in the treatment of nervous system diseases. Auricular Vagus Nerve Stimulation has become one of the research hotspots in this field, because there is no implantation risk. However, there is no unified standard for the treatment parameters of aVNS for nervous system diseases. In this paper, the research progress of the anatomical structure and parameters of the vagus nerve and its role in nervous system diseases are reviewed to provide basis for further research.

Keywords

Auricular Vagus Nerve Stimulation, Nervous System Diseases, Review

1. Introduction

Vagus nerve stimulation is a kind of neuroregulation technology. Since it was approved by FDA for the treatment of refractory epilepsy and chronic depression in 1997, it has attracted more and more attention from researchers and clinical scholars. By 2018, more than 100,000 patients around the world had received this implant surgery [1]. Although it is a minimally invasive procedure, the process of implanting the electrodes requires stripping the cervical vagus nerve trunk away from the carotid artery. Thus, surgical intervention may result in potential adverse events, such as tachyarrhythmic arrhythmias, peritracheal hematoma (due to surgical trauma), and other serious complications, including vocal cord dysfunction and dyspnea (due to nerve damage). In addition, due to the high cost of implant equipment and other reasons, the clinical application of this treatment is severely limited.

In recent years, with the development of neuroanatomy, the focus of research on vagus nerve stimulation has shifted from implantable stimulation to non-implantable stimulation. Non-implantable stimulation can be divided into transcutaneous cervical vagus nerve stimulation and ear vagus nerve stimulation according to its targets. Among them, auricular vagus nerve stimulation is popular because of its low side effects and low cost. It is one of the hot topics of vagus nerve research at present, especially the application of this technology in nervous system diseases. Starting from the nervous system, this review summarizes the anatomical progress of auricular vagus nerve, the treatment of nervous system diseases and the research status of stimulation parameters, etc., and puts forward suggestions for future research direction.

2. Neuroanatomy of the Auricular Vagus Nerve

2.1. Autopsy

The development of microanatomy provides the basis for the study of auricular vagus nerve (ABVN). The earliest autopsy literature on the ear vagus nerve can be traced back to 1993. Ueno [2] found that a branch of the vagus nerve and a branch of the facial nerve jointly supplied the back of the outer ear by dissecting three corpses. In 1998, Tekdemir [3] observed ABVN in the external auditory canal of all 16 human ear specimens, but due to technical conditions, it is still impossible to make an accurate skin map of the distribution of the vagus nerve in the ear. It was not until 2002 that German researchers Peuker & Filler [4] conducted a fine dissection of 14 external ears and found that the vagus nerve mainly distributed in the ear ring, tragus and conchae, and created a relatively complete skin map. This landmark discovery was the clinical application of the vagus nerve. In particular, the selection of intervention targets provides anatomical basis. Subsequently, Kiyokawa [5] and Watanabe [6] further described the distribution of small branches of the auricular vagus nerve and the regularity of their passage through the skull. A recent study showed that all the nerve fibers in the pinna are located between the ear cartilage and the skin at a depth of 1 - 1.5 mm from the skin surface. Autopsy is the "gold standard" method for studying the skin distribution map of auricular vagus nerve. However, the number of relevant literatures is limited currently, which may be related to the small diameter of auricular vagus nerve and the low popularity of microanatomical equipment for head and neck.

2.2. Classification of Nerve Fibers

According to their diameter, vagus nerve fibers can be divided into three types: type A (composed of Aα, Aβ, Aγ, and Aδ), type B, and type C. Different types of nerve fibers have different diameters and different thickened myelin sheaths, which correspond to different conduction velocities, and usually nerve fibers with thicker myelin sheaths are associated with faster conduction velocities or stronger signal propagation. The ear vagus nerve is a sensory fiber. It is one of

the few branches of the vagus nerve that does not contain motor fibers. Therefore, the myelinated nerve fibers found in ABVN are considered to be type A sensory fibers. Currently, only the Safi [7] study has determined the number of myelinated nerve fibers present in the ear vagus nerve: about 50% of these myelinated fibers are between 2.5 and 4 μm in diameter, indicating that they belong to the Aδ class, Nearly 20% of the fibers were >7 μm in diameter, indicating that these fibers belong to the Aβ class. Thus, low intensity stimulation during electrical stimulation can activate the auricular vagus nerve.

2.3. The Heterogeneity of the Distribution

Up to now, the uniform distribution of sympathetic axons in the auricle skin has not been comprehensively studied. Only one study on the human ear explored the distribution of the auricle region. Cakmak [8] found that the distribution of sympathetic neurotransmitters around the blood vessels in the auricle region was more intensive through immunohistochemical labeling technology, and such sympathetic markers were mainly concentrated in the upper part of the auricle region (auricle boat). This finding explains why most current studies on otovagus place false electrodes/stimulators in the lower part of the auricle. In addition, the location of auricular artery perforation is also worth studying, because high density sympathetic axon tracts are distributed in the auricular skin area of the perforated artery. Currently, there are 5 locations of artery perforation in the auricular, from top to bottom, respectively, triangular fossa, auricular sheath, foot of auricular wheel, auricular cavity and antitragus. Therefore, the location of artery perforation should be considered when designing the placement area of the stimulator.

3. Research Status of Therapeutic Parameters of Auricular Vagus Nerve Stimulation

Ventureyra [9] first proposed the concept of transcutaneous ear vagus nerve stimulation by combining electrical nerve stimulation methods, anatomical basis of auricular vagus nerve and acupuncture. Thereafter, researchers have been refining and optimizing vagus nerve stimulation parameters to treat various neurological diseases. The current complete description of the parameters of vagal therapy includes pulse width, current intensity, frequency, on/off time ratio, and duration.

A recent study [10] analyzed the therapeutic parameters of 22 clinical studies on auricular vagus nerve stimulation, and summarized the most common parameters of the therapeutic nervous system and the range of parameter Settings. For example, pulse width: 250 μs is most commonly used, and the setting range is 20 - 250 μs; The frequency is most commonly 25 Hz, and the setting range is 1 - 30 Hz; on/off time ratio: the most commonly used for 30 s on, set range 0.5 s - 30 min on /30 - 270 s off; Current intensity: Most commonly used for above threshold stimulation, setting range 0.13 - 50 mA. In addition, the authors also summarized the parameters of different experimental animals, such as rats: pulse

width set range of 100 μs - 4 ms, frequency set range of 2 - 300 Hz, switching time ratio: 125 ms - 30 min on/17.5 s - 5 min off, current output intensity of 0.2 - 10 mA.

Early study [10] on VNS parameters mainly focused on the on/off time, in order to avoid direct damage caused by long-term nerve stimulation, while to meet the requirements of saving power and improving the battery life of implants. When it comes to aVNS research, the safety and power issues of implantable VNS have been resolved because the external pulse stimulator will not be influenced by power issues or does not require direct nerve stimulation either. However, some animal experiments [11] pointed out that the on/off time had little effect on neural plasticity, while the pairing combination of stimulus-combined behavioral intervention in terms of intervention time may have a dose-effect relationship. Two clinical studies [12] [13] further verified this conclusion. At the present stage, researches on parameter selection focus on the exploration of current intensity and pulse width, because it has been observed in experiments that the increase of current intensity can gradually up-regulate the release of neurotransmitters such as norepinephrine [14] and increase the power generation frequency of locus leuculeus cells [15]. Another study [16] confirmed the interaction between current intensity and pulse width. When current intensity is equal, increasing pulse width can improve the VNS effect. However, in the study of nervous system diseases, no matter in experimental animal studies or human experiments, the selection of frequency parameters ranges from 1 to 300 Hz, and there is no optimal recommended parameter, while 25 Hz is the most commonly used. In addition, studies on the correlation between frequency parameters and behavioral effects were all conducted in the 1990s [17], so it is necessary to optimize frequency parameters.

4. Application of aVNS in Common Diseases of Nervous System

4.1. Epilepsy

Nearly 70 million people over the world are affected by epilepsy. Among these, more than 75 percent of people with epilepsy do not receive medication, and about one-third of those who do receive medication but fail to effectively control their symptoms. A large number of studies have shown that VNS is an effective treatment for intractable epilepsy in adults. Both VNS and aVNS can reduce epileptic seizure in rats by activating the firing of neurons in NTS [18]. Zagon [19] suggested that hyperpolarization mediated by vagus nerve could reduce the excitability of cortical neurons, which was the reason for the suppression of epileptic seizure. In addition, aVNS can inhibit cortical synchrony and rhythmicity in rats [20]. Regarding the duration of effect, the duration of anti-epileptic action of VNS and aVNS is similar [21]. In clinical studies, aVNS has been repeatedly verified to reduce the frequency, intensity and duration of epileptic seizures [22] [23] [24], as well as reduce the use of antiepileptic drugs [25].

In terms of parameter research: Clinically, He [18] *et al.* selected aVNS with a frequency of 20 Hz, 30 min each time, three times a day for 6 months, and the results suggested that the frequency of seizures was reduced by 54% after 6 months. Liu *et al.* [26] found that after 6 months of aVNS treatment, the frequency of seizures in 16 out of 17 patients was reduced by 64.4% on average. The parameter selection was different from the previous experiment, 20 min each time, three times a day for 6 months, but the stimulation frequency was 10 Hz. In animal studies, 20 - 30 Hz is the most common intervention parameter [27] [28]. Woodbury *et al.* proposed the optimal parameters range of 500 - 1000 μs, 60 sON time, and 0.2 - 0.5 mA in a study comparing the antiepileptic effect in rats [29].

4.2. Depression

The main symptoms of depression are persistent depression and anhedonia, often accompanied by anxiety. Currently, more than 264 million people worldwide suffer from depression, and rates of morbidity, morbidity, suicide and relapse are rising, while cure rates are relatively low. There is more and more evidence proofing that aVNS can improve depressive symptoms in adult patients and reduce self-rated depression scores [30] [31] [32]. In terms of mechanism research, Li *et al.* [33] believe that melatonin secretion improves depressive behavior in diabetic rats, and its effect may be related to the downregulation of hypothalamic-pituitary-adrenal axis [34].

In terms of parameter studies, Hein *et al.* [31] demonstrated that aVNS for 2 consecutive weeks could significantly improve the results of Baker Depression Scale (BDI; 27.0 - 14.0), but no significant change was observed on the Hamilton Depression Rating Scale (HAMD). The stimulation parameters provided in this paper are incomplete: 1.5 Hz unidirectional rectangular wave, current Settings described as patient-acceptable range (0 - 600 mA). Fang *et al.* [35] showed that aVNS could improve the results of patients' HAMD, self-rated anxiety scale SAS, and self-rated depression scale SDS, and inferred through fMRI analysis that its effect might be due to the adjustment of the resting state functional connectivity of the default mode network. Again, stimulus parameters were not described in detail, 20 Hz, dense wave, wave width <1 ms, and output intensity was adjusted according to patient tolerance (4 - 6 mA).

4.3. Apoplexy

The morbidity, disability and mortality of stroke globally are on the rise, placing a huge economic and social burden on the world. This causes approximately 5.5 million deaths per year and is one of the three major causes of death, of which approximately 50% of survivors develop chronic disability [36]. Previous studies have found that aVNS can significantly reduce infarct volume after cerebral ischemia and improve nervous system scores in rats [37]. Jiang *et al.* [38] reported that in addition to reducing cerebral infarction size and improving neurological function, aVNS also believed that its therapeutic effect was related to

the increased expression of angiogenesis and angiogenesis factors in ischemic penumbra. In addition, in some clinical reports, Capone [39] pointed out that aVNS combined with robotic rehabilitation therapy can improve the upper limb function of stroke patients and bring long-term benefits for stroke rehabilitation, which is similar to the results of two recent clinical trials [40] [41]. From basic research to clinical reports, it is suggested that aVNS is a potential method for post-stroke rehabilitation.

In terms of parameter studies, Porter [42] and Engineer [43] believed that intervention of 100 μs, 30 Hz, 500 ms, 0.8 mA had a positive effect on the improvement of neurological function in apoplexy rats. In two studies of Hays [11] [44], different pulse widths were selected, both of which showed significant differences in the improvement of upper limb motor function of rats by VNS paired rehabilitation training, and further confirmed the importance of stimulus dose and therapeutic response. In addition, in the study of single stimulation time, compared with 180 s stimulation, the therapeutic effect of 30 s of short time stimulation is more ideal, that is, when the application of too high sustained stimulation intensity will make the nerve plasticity effect disappear. In the study of frequency intensity, medium frequency stimulation is superior to high frequency (120 Hz) and low frequency (7.5 Hz) stimulation [45]. In terms of parameter combination studies, two studies have considered the interaction between pulse width and current intensity and found that both can partially compensate each other [46]. Of course, other studies also used different stimulation parameters [37] [38] [47] [48] [49], such as: 25 Hz, 0.5 ms, 0.5 mA, 30 s for a single stimulation, 5 min interval, and 1h duration, which also had the ability to improve the motor ability of stroke rats and reduce the volume of cerebral infarction.

4.4. Anxiety

Anxiety is a common mental illness. Approximately one in four people worldwide has or has had an anxiety disorder [50]. Prevalence ranges from 4.8% in China to 31% in the United States [51]. aVNS stimulation with 25 Hz, 0.5 mA, and 30 s parameters has been shown to accelerate the resolution of conditioned fear, but this effect can only be maintained for about 24 hours after stopping treatment [52]. However, Genheimer *et al.* [53] did not come to a positive conclusion that aVNS could not inhibit conditioned fear, which was inconsistent with the results of previous studies, and concluded that the stimulus scheme used in the experiment (25 Hz, 250 μs, 0.1 mA, 10 s) may need to be improved. Therefore, whether aVNS can treat anxiety and prevent its recurrence is controversial and needs to be studied with perfect parameter combination setting. In most of the animal experiments, 0.4 mA, 20 Hz and 100 μs were used, for 30 seconds. These parameters have been repeatedly confirmed to be beneficial to the elimination of conditioned fear in rats [54] [55] [56].

4.5. Traumatic Brain Injury

Traumatic brain injury refers to direct or indirect brain injury caused by exter-

nal violence. Severe traumatic brain injury can lead to prolonged coma or even death. Many studies have shown that aVNS can improve the score of Coma Recovery Scale (CRS-R) in patients with traumatic brain injury [57] [58], especially the score of the exercise scale [59] [60]. Yu [61] was the first to report that patients with post-TBI consciousness disorder achieved eye opening after aVNS treatment, and speculated that its function was to adjust the sleep-wake cycle by enhancing the functional connectivity of DMN. In animal studies, Sharon [62] reported that aVNS induced brain arousal, including temporary dilation of the pupil and reduced occipital alpha oscillations. In short, these results suggest that aVNS holds promise in the treatment of traumatic brain injury and disorders of consciousness. In terms of parameter setting, different parameter combinations are adopted in different TBI models, which all have positive effects. For example, fluid impact model (30 s, 0.5 mA, 20 Hz) [63] [64] [65] [66], heavy object impact model (10 min, 2 mA) [67] and detonation damage model (10 V, 5 Hz, 5 ms, 20 min) [68].

4.6. Others

In the study of mental disorders, Cimpianu *et al.* [69] and Jin *et al.* [70] consider aVNS as a treatment for autism spectrum disorders and many other mental disorders, but a clinical study found that aVNS failed to improve the symptoms of schizophrenia patients [71]. With the development of aVNS research, the scope of aVNS treatment has been expanded to include cognitive impairment and memory ability. It has been reported that aVNS increased associative memory in the elderly [72] and improved learning ability in adults [73], but not non-verbal memory [74]. A recent animal study [75] showed that aVNS stimulation led to significant improvements in memory in Fmr1 knock-out mice.

5. Summary and Prospect

Many experts recommend that adequate studies be done to map the dose-response curve of a new treatment before it can be translated into the clinic. Although otovagus nerve stimulation has been widely regarded as a potential neuroregulatory technique, especially for neurological diseases, the research on the dosing effect of aVNS still needs to be optimized and improved. First, dose-effect study of different types of nerve fibers. Autopsy studies support the use of the auricular concha region as the stimulation site of the vagus nerve on the body surface. Meanwhile, studies on the characteristics of various types of nerve fibers of the vagus nerve further clarify the anatomical basis of its effectiveness. However, at present, the research on the relationship between the response strength of different types of vagus nerve fibers to stimulation and biological effects is very limited, and there is a large space for exploration. Second, the dose-effect study of parameters. Although the screening results of aVNS therapeutic parameters dose and effect for some diseases have been reported in numerous literatures, they tend to focus on current output intensity, pulse width and switching time, etc.,

with little exploration on frequency setting. In addition, the current research related to frequency conversion stimulation has gradually become a hot topic in the field of neuroregulation. Therefore, the concept of frequency conversion can be considered for innovative expansion in the future research on parameter optimization of aVNS. In addition, there are interactions among parameters of physical stimulus, such as coordination, balance, cancellation and compensation, etc., so the differences of pairing and combination of parameters should be considered in future research design in order to fully solve the limitations of single-parameter research.

In addition, the research field of the non-uniformity of auricular surface nerve distribution still needs to be further explored to improve the depiction of auricular nerve distribution, which is conducive to the selection of stimulus targets and pseudostimulation regions, and also meets the development needs of precision medicine. In terms of the application prospect of the treatment of neurological diseases, aVNS has been expanding the spectrum of diseases, but some conclusions are still controversial. Therefore, it is necessary to improve the quality of research to present higher strength evidence to verify its effectiveness.

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Author Contributions

Jiaen Yang and Ning Jia contributed equally to this work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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