Review Article

Vagus nerve stimulation in neurological diseases

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Abstract

Evidence from clinical and experimental research suggests that neurological diseases may affect the autonomic nervous system. Vagus nerve, the main component of the parasympathetic nervous system, provides the regulation of parasympathetic effects on the smooth muscle of the upper respiratory tract, gastrointestinal tract and heart. It has been used in the treatment of epilepsy and depression for years. In recent years, it has been showed that vagus nerve stimulation (VNS) can also be used in the treatment of Alzheimer's disease, Parkinson's disease, migraine and other disorders. Thus, it is crucial to understand the peripheral anatomy and physiology of the vagus nerve and how VNS reduces or eliminates these diseases. The molecular mechanism beyond this method needs to be elucidated with further studies. Therefore, in this review, it is planned to investigate the role of VNS method in neurological diseases.

Keywords: epilepsy, multiple sclerosis, neurology, vagus nerve stimulation

Introduction

The vagus nerve is a major component of the autonomic nervous system, it has an essential role in the regulation of metabolic homeostasis and plays a key role in the neuroendocrine-immune axis to maintain homeostasis through its afferent and efferent pathways. Vagus nerve stimulation (VNS) refers to any technique that stimulates the vagus nerve, including manual or electrical stimulation [1]. VNS is currently approved by food and drug administration (FDA) for therapeutic use in patients aged >12 years with drug-resistant epilepsy and depression [1,2].

Epilepsy is a neurological disorder characterized by abnormal discharges in neurons. It is known that cardiac and respiratory disorders are also accompanied by epilepsy especially in drug-resistant patient groups after a certain age. Therefore, it is stated that the autonomic nervous system is affected in epilepsy but the treatment is not clear [1].

The autonomic nervous system is primarily activated by regions located in the spinal cord, brain stem and hypothalamus. In addition, segments of the brain cortex, particularly the limbic cortex, can transmit signals from the brain to the spinal cord and the brain stem. This
transmission may affect autonomic control. Epilepsy is a chronic disease characterized by recurrent neuron discharge caused by the cerebral cortex. The relevance of neurological diseases and autonomic nervous system centers will provide the basis for new studies in terms of the treatment of the disease by illuminating the molecular mechanism.

Parasympathetic stimulation effects of the autonomic nervous system may be briefly listed in several physiological conditions such as contraction in the muscles of the eye, contraction of heart muscle and heart rate, dilatation of coronary arteries. These features provide the vagus nerve to control the contraction mechanism of the heart muscle with parasympathetic effect. In line with this objective, the vagus nerve is a “bridge” between the brain and the heart and it releases the acetylcholine (ACh) to our body for providing calm via parasympathetic effect [2]. Today, the parasympathetic effect in the related region is increased or suppressed by drugs [3]. It has also been suggested in the literature that this stimulation may reduce the abnormalities in brain activity.

It is crucial to understand the peripheral anatomy and physiology of the vagus nerve and central afferent projections how VNS effects and it is applicable in pediatric epilepsy cases. Further investigations have been proposed to investigate this phenomenon, particularly in patients with sleep apnea syndromes or dangerous respiratory function [7]. In a 2003 review, published evidence of changes in mood and cognition of VNS-related changes in patients with neuropsychiatric disorders was evaluated. Conflicting results suggest that VNS has a positive psychotropic effect in patients with refractory epilepsy and depression. Although the data on cognition are not clear, it is stated that the first results of the pilot studies in Alzheimer’s disease are promising [8]. In the 2008 study, the comparison of corpus callosotomy and vagus nerve stimulation was performed in children with LGS. According to the results, it has been reported that VNS treatment parameters are more effective and safer for children with LGS disease as a result of temporary complications [9]. Overall, it might be said that VNS methodology has no side effects and it is applicable in pediatric epilepsy cases.

The effect of VNS on amygdalo-hypothalamic and amygdalo-bulbar regions was investigated in 2010. It has been reported that the inhibitory effects obtained may contribute to the therapeutic effect of this stimulation in the treatment of epilepsy and related visceral disorders [10]. In 2011, the effects of VNS on pro- and anti-inflammatory cytokines in peripheral blood were investigated in refractory epilepsy. It resulted in a rebalancing of the VNS immune system. It has also led to a neurotoxic reduction and increased metabolites of neuroprotective kynurenine and, finally, normalization of cortisol levels [11]. By these two studies, the significant molecular effect of VNS has been evaluated.

A randomized study was conducted to evaluate the efficacy of transcutaneous VNS and control stimulation in drug-resistant epilepsy patients in 2016. As a result of the method applied to the groups as 1 Hz and 25 Hz, there was no significant difference between the two groups. It has been shown that transcutaneous VNS might be used as a treatment method for resistant epilepsy [12]. In 2016, it was aimed to explain the acute effects of VNS on attention, cognition and emotional reactivity in epileptic patients. In the results, it was observed that VNS increased brain responses similar to increased attention and improved working memory performance [13]. In a case report published in 2017 to demonstrate the effects of VNS on refractory status epilepticus, VNS method was applied to a 67-year-old
patient who was in a coma. At the end of two weeks, the VNS method was found to be an essential treatment modality for status epilepticus in patients who became fully functional and reached all the conditions [14].

In 2017, VNS treatment effects were observed in patients with Dravet syndrome in addition to normal treatment. A reduction in seizure frequency was observed in 68 patients as a result of controlled trials [15]. In a study conducted in 2018, children with resistant status epilepticus were compared before and after VNS device implantation and those who had reduced the Parent Stress Index scores, especially those with reduced seizure frequency. The results of the study showed that VNS not only reduced the frequency of seizures but also reduced the psychological burden on children with resistant epilepsy [16]. In 2018, a study was conducted to investigate the effect of VNS on status epilepticus in children. As a result of the study, it was observed that VNS had a significant effect on widespread convulsive seizures in children with status epilepticus and refractory epilepsy [17]. The interregional metabolic association of VNS and positron emission tomography (PET) was investigated in 2018 for pediatric patients with epilepsy. In pediatric patients with VNS implanted with refractory epilepsy, the prognostic role of patients with preoperative refractory epilepsy and seizure control was investigated and significant results were obtained for VNS [18]. In a 2019 case report, the effects of VNS on super-refractory status epilepticus were shown. Acute termination of status epilepticus after 72 hours of VNS added strong evidence that the use of VNS for refractory status epilepticus was beneficial [19].

In 2019, a risk profile was compiled for adults using VNS by multicentric patient data from an international database. In this study, presenting an up-to-date view of the risks and outcomes in VNS, which revealed a safe risk profile for 30 days, it was reported that VNS might be useful [20]. By recognizing epilepsy as a network disease that disrupts the ability of the brain networks to rest, VNS may control epileptic seizures through functional link modulation.

Alzheimer’s disease
Alzheimer’s disease (AD) is a chronic and progressive neurodegenerative disease which is characterized by the accumulation of amyloid-beta plaques (Aβ) and neurofibrillary tangles (NFTs) in the brain. Memory loss is among the first clinical symptoms complained by patients suffering from AD with an impact on daily activities. Acetylcholine represents a major transmitter in the brain and cholinergic deficits occur during the disease progression, leading to widespread cognitive dysfunction and decline. According to the relation of the vagus nerve and ACh, it is expected that VNS methodology might be useful in AD cases. At last decades, it has been started to study and significant results have been observed.

In a 2004 review, published evidence of changes in mood and cognition of VNS-related changes in patients with neuropsychiatric disorders was evaluated. Conflicting results suggest that VNS has a positive psychotropic effect in patients with refractory epilepsy and depression. Although the data on cognition are not clear, it is stated that the first results of the pilot studies in AD are promising [8]. In 2006, the relationship between VNS and cognition was investigated. Preliminary results emphasized that VNS was promising in the treatment of diseases associated with cognitive decline such as AD [21]. In a study conducted in 2017, microglial modulation directed to VNS was investigated in experimental Alzheimer’s model. As a result of the experiments, significant morphological changes were observed in the microglia following VNS. It has also been shown that the morphological markers of microglial aging might be reversed by VNS [22].

Parkinson’s disease
Parkinson’s disease (PD) is a neurological disorder associated with loss of dopaminergic neurons in the substantia nigra and Lewy bodies. Lewy bodies are aggregated proteins that develop inside nerve cells abnormally. In recent years, studies show that VNS might be a potential treatment method for PD.

In 2017, the therapeutic potential of VNS was evaluated in the experimental Parkinson model. The results have shown that VNS has a strong therapeutic potential for Parkinson’s disease, with beneficial effects on noradrenergic neurons of locus coeruleus and dopaminergic neurons in substantia nigra [23].

In a 2018 study, the effects of auricular vagus nerve stimulation (aVNS) on the substantia nigra (SN) and dopaminergic neurodegeneration were investigated by Parkinson’s rat model. The results showed that aVNS decreased T helper (Th) 17 cells while increasing the number of regulatory T (Treg) cells. In addition, aVNS was thought to have neuroprotective effects against dopaminergic damage, possibly by suppressing the development of inflammation and by modulating innate immune responses [24]. Therefore, it is predicted that VNS may be a potentially promising treatment in the future for Parkinson disease.

Depression
Depression is a highly common clinical syndrome in recent years. Patients with depression have a feeling of sadness and diminished stress. Recent studies showed that VNS is a highly effective method for patients with depression.
In 2001, VNS was applied to 60 patients with treatment-resistant major depressive episodes and it was aimed to determine the clinical results. In conclusion, the evidence for the long-term therapeutic benefits and tolerability of VNS has been predicted to be critical in determining the role of treatment-resistant depression [25]. In a 2002 study on depressive patients, VNS showed promising results for adults in a treatment-resistant major depressive episode [26]. In a case report published in 2005, a patient with a refractory depression of the VNS implant was required for the first time after a very long period (69 months) of regeneration and the patient continued to have routine VNS treatment after the replacement of the implant [27]. With the results obtained, long-term VNS treatment provided continuous symptomatic benefit and functional development.

In a 2004 review, published evidence of changes in mood and cognition of VNS-related changes in patients with neuropsychiatric disorders was evaluated. Although the data on cognition are not clear, it is stated that the first results of the pilot studies in AD are promising [8]. In 2004, a study was conducted to investigate the anti-depressive effects of VNS in mice. According to this study, VNS has been shown to be key to understand the anti-depressive mechanism, to improve treatment and to select the best surgical procedure, and to be effective in an approved antidepressant activity test of VNS [28]. Conflicting results suggest that VNS has a positive psychotropic effect in patients with refractory epilepsy and depression.

In a 2005 study, changes in regional cerebral blood flow caused by VNS were investigated. The results indicated that VNS treatment showed similarities with antidepressant pharmacotherapy in depression treatment [29]. One year later, it was aimed to observe the change in cerebral blood flow in patients undergoing VNS in depression. Four resistant major depression patients undergoing VNS treatment were also subjected to positron emission tomography screening. As a result of the study, bilateral temporal cortex and right parietal region were significantly decreased [30]. It was reported that the change regions correspond to the brain structures associated with depression and the afferent pathways of the vagus nerve.

In 2007, a discussion from the New England Journal of Medicine suggested that VNS could be used for depression [31]. In 2008, chronic VNS for treatment-resistant depression was reported to reduce ventromedial prefrontal glucose metabolism [32]. Overall, VNS may be used as a treatment in depression cases and it has a positive effect on glucose balance.

The effects of VNS treatment on treatment-resistant bipolar depression and unipolar depression in 2008 were compared. As a result, the short- and long-term effects of VNS were found to be similar [33]. In another study, it was emphasized that the VNS method applied in treatment-resistant depression patients could be an alternative treatment and economically more suitable [34]. In 2008, VNS treatment was recommended for workers with depression in Europe and successful results were obtained in the first trials [35]. Because VNS is useful in depression and cheaper than other methodologies, it may be used on depressive work types.

In 2010, a two-year evaluation of VNS was made in treatment-resistant depression. Accordingly, it has been determined that there are a positive clinical response and a relatively benign side effect profile among patients with treatment-resistant depression [36]. In resistant cases, VNS might also be tried as an alternative methodology.

In a 2015 study on the antidepressant-like effects of VNS, noradrenergic locus coeruleus neurons were selectively lesioned to test for their participation in the antidepressant-like effect of VNS in forced swimming testing. The results showed that noradrenergic neurons from locus coeruleus play an essential role in the antidepressant-like effect of VNS [37]. In 2015, a report of five years of treatment of five patients who underwent VNS implant for resistant depression was presented [38]. In these case series, it has been shown that VNS could decrease the severity of depression even on resistant cases.

### Migraine

Migraine is a disorder leading to people to suffer from daily headache. Several therapies and drugs are available for migraine treatment but these are only for acute attacks and non-refractory migraine. For chronic and refractory migraine, recent studies showed that VNS might be an effective method.

In one case published in 2003, implanted VNS for refractory seizures was predicted to reduce pain in patients. As a result, it has been reported that VNS may be useful for the prophylactic treatment of migraine [39]. In 2005, VNS was shown to be an effective treatment for drug-resistant epilepsy and depression, as well as analgesic effects [40]. In 2015, it was aimed to evaluate the efficacy and safety of transcutaneous stimulation of the auricular branch of the vagal nerve in the treatment of chronic migraine. On the days after 12 weeks of treatment, the decrease in mean headache was higher than that reported for other nerve stimulation procedures and this result showed that VNS had an important place in the treatment of chronic migraine [41]. A research was conducted in 2015 about the role of neurostimulation in migraine. Chronic headaches characterized by daily headache affect almost 3% of the general population. Invasive and non-invasive central and/or peripheral neurostimulation techniques have been developed by different research groups with encouraging results for a different type of headaches. In this article, the acute effect of non-invasive vagus nerve stimulation (nVSSS) was evaluated to treat migraine attacks in a patient population affected by high-frequency episodic migraine or chronic migraine [42]. Based
on these, the idea that VNS plays a role in the treatment of severe refractory headaches has been proposed. As a result, it has been suggested that VNS may be an effective therapy for persistent chronic migraine pain.

In a 2016 study, the cost-effectiveness of non-invasive VNS was analyzed in the treatment of chronic headache [43]. In a review of VNS in the treatment of headache in 2016, non-invasive VNS was reported to be as effective as any other invasive alternative. With a strong potential therapeutic benefit and high safety profile, further development and implementation of VSS has been shown to be promising [44]. As a result of the study, it was predicted that treatment with VNS was more economical and safer for migraine cases.

Other disorders

There are more disorders that researchers think VNS might be helpful such as anxiety, obsessive-compulsive disorder, cerebral ischemia, amyotrophic lateral sclerosis, autism and postoperative cognitive dysfunction. Further studies are required to understand the mechanism underlying and to develop treatment strategies.

According to a review published in 2002, it was possible to stimulate brain activity and related behaviors by VNS on the neck. From this point of view, it is stated that there are potential VNS research opportunities for both clinical and basic researchers to review the neurobiology in VNS to emphasize the clinical findings of VNS so far [45]. In 2008, VNS pilot study was conducted for treatment-resistant anxiety disorders. Acute and long-term improvement was observed in patients. Accordingly, the role of VNS in the treatment of anxiety disorders, especially in the treatment of the obsessive-compulsive disorder is required [46]. In a study conducted to investigate the effects of VNS on fear and anxiety in 2018, it was observed that VNS method could significantly affect fear and anxiety levels [47]. It might be said that VNS methodology needs pre-clinic studies for application on anxiety disorders.

The role of lipocalin prostaglandin D2 synthase (L-PGDS) in brain ischemia has not been fully elucidated to date. For this reason, in 2016, it was investigated the mediated neuroprotection of VNS in the rat model of L-PGDS. This study investigated the role of L-PGDS in the brain and whether this process played a role in the VNS-mediated neuroprotection mechanism [48]. Overall, the results show that L-PGDS is a potential mediator of VNS-induced neuroprotection against damage.

In the 2008 study, 1-year VNS treatment was applied in drug-resistant bipolar disorders. The results showed that VNS treatment gave significant results in this disease and it was a good treatment option [49]. Because the number of patients in this study is low, VNS treatment should be performed in more powerful patient groups for bipolar disorder.

In 2009, it was discussed that transcutaneous VNS mightly decrease postoperative cognitive dysfunction in elderly patients [50]. In another study conducted in 2018, it was investigated whether aVNS protected against postoperative cognitive dysfunction by reducing neuroinflammation and neurodegeneration in elderly rats. It is suggested that non-invasive aVNS might be a promising method for clinical treatment in such disorders [51]. Gerontological studies show that VNS might be useful for elder people.

For other rare cases such as cerebral ischemia, amyotrophic lateral sclerosis and autism, there are few studies showing VNS treatment is useful. More studies will be helping the power of VNS in these cases. As examples, there are three studies. First, it was investigated whether VNS decreased infarct size in rat focal cerebral ischemia and a potential role was played for cerebral blood flow (CBF). In this study, it was investigated that the infarct-reducing effect of VNS mediated CBF increase and significant results were found [52]. Secondly, in a study conducted in 2018, the effects of intraoperative VNS on gastrointestinal microbiome were investigated in a mouse model of amyotrophic lateral sclerosis. Accordingly, it was emphasized that different stimulation parameters or the use of chronic VNS were crucial [53]. Finally, in 2018, neuromodulation of autism spectrum disorders (ASD) was investigated by using VNS. There is some evidence that VNS might improve behaviors in people with ASD as applied for epilepsy [54]. Although more stringent studies are needed, there are indications that this occurs independently of seizure frequency and the effects on mood.

Conclusion

Vagus nerve stimulation has recently been used as a complementary treatment method. In neurological diseases, it is an increasingly preferred method. It is applied directly to cognitive disorders such as epilepsy, Alzheimer's disease, Parkinson's disease or depression. In recent studies, it has also been found to be applied in migraine. In comparison, VNS methodology is more powerful in epilepsy cases than other neurological diseases. Reducing the seizure effect and controlling epilepsy make the VNS necessary in epilepsy cases. Considering that neurological diseases affect the autonomic nervous system, it is recommended that the VNS evolves in accordance with the molecular mechanism of the disease.

Biochemical parameters that are affected by vagal nerve such as norepinephrine, serotonin, GABA and dopamine should be investigated by modeling each animal models separately for each disease. This modeling is going to help clarifying the mechanism of VNS. Furthermore, the axon size of myelinated and unmyelinated fibers and the myelin thickness with the myelinated ones also need to be elucidated. This evaluation may explain the possible impact mechanism of VNS on neurological disorders. Accordingly, VNS application

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frequencies can be adjusted more precisely. It is also more economic than other applied methodologies. As a conclusion, VNS is a treatment method which is used in neurological diseases and it has significant results.

**Conflict of interest**
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**References**
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