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Vagus nerve stimulation as a promising adjunctive treatment for ischemic stroke

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ABSTRACT

The Food and Drug Administration has approved vagus-nerve stimulation (VNS) for the treatment of patients with epilepsy, depression, and headache. By targeting diverse neuroprotective and neuroplasticity pathways, VNS has the potential to be expanded as a treatment for ischemic stroke. VNS has been found to attenuate infarct volume, reduce neurological deficits, and improve memory and cognition in rats with stroke injuries. Some pilot studies with small sample sizes suggested that VNS paired with rehabilitation can be a promising approach to improve limb motor function in chronic-stroke patients. In this review, we first provide an overview of the diverse effects of VNS in the post-stroke condition, followed by a thorough discussion of the potential mechanisms responsible for its neuroprotective and neuroplasticity-enhancing properties. We also outline the clinical applications of the recently emerging non-invasive VNS. Finally, we summarize the advantages and adverse effects of the current VNS applications, as well as the future challenges and directions for the clinical implementation of VNS in ischemic stroke. Although more fundamental and clinical research is still required to fully understand its mechanisms of efficacy, we believe that the frequent and successful clinical use of VNS as a treatment for ischemic stroke is well within reach.

1. Introduction

Ischemic stroke is a leading cause of disability and death worldwide, causing a heavy economic burden to family, society, and government. The current treatments for acute ischemic stroke include both intravenous thrombolysis and mechanical thrombectomy (Xiong et al., 2019). Important advances regarding both treatment modalities have occurred recently. However, only 10% or fewer patients are within the appropriate time window to be eligible for these treatments, which limits their further clinical applications. Therefore, a novel adjuvant therapy would be valuable to stabilize patients suffering from ischemic stroke.

Neuroprotection is a target of adjunctive treatments for thrombolysis, specifically in the cerebral parenchyma during the acute ischemic phase. Furthermore, improving neuroplasticity to restore neuronal function is a supplementary therapy during the chronic rehabilitation phase in those patients with significant impairment. Ideally, the future treatment plan for ischemic stroke will encompass a combination of thrombolysis, anti-thrombotics (for secondary prevention), neuroprotection (to stabilize the penumbra), as well as strategies to enhance neuroplasticity (Moretti et al., 2015).

The vagus nerve (VN), one of the components of the autonomic nervous system, comprises an intricate neuro-endocrine-immune network that maintains metabolic homeostasis and regulates diverse cerebral physiological or pathological processes, including stroke (Mravec, 2010). With reciprocal neural connections to multiple brain regions, the VN serves as a carrier of input and output that integrates interoceptive information and responds with appropriate, adaptive, and modulatory feedback (Yuan and Silberstein, 2016a). Vagus-nerve stimulation (VNS) refers to any technique that stimulates the VN (Howland, 2014) (Fig. 1). VNS has recently been explored as a promising therapy that targets many different neuroprotective and neuroplasticity pathways and

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Abbreviations

α7 nicotinic acetylcholine receptor α7 nAchR
Adenosine triphosphate ATP
Alzheimer's disease AD
Auricular branch of the vagal nerve ABVN
Blood brain barrier BBB
Brain-derived neurotrophic factor BDNF
Central nervous system CNS
Cholinergic anti-inflammatory pathway CAIP
Dentate gyrus DG
Dorsal raphe nucleus DRN
Food and Drug Administration FDA
Functional magnetic resonance imaging fMRI
Growth differentiation factor 11 GDF11
Interleukin IL
Ischemia/reperfusion I/R
Locus coeruleus LC
Non-invasive VNS nVNS
Norepinephrine NE
Nucleus tractus solitarious NTS
Oxidative stress OS
Peroxisome proliferator-activated receptor γ PPARγ
Reactive oxygen species ROS
Sphenopalatine ganglion SPG
Transcutaneous auricular vagus nerve stimulation taVNS
Transcutaneous cervical vagus nerve stimulation tcVNS
Tumor necrosis factor α TNF-α
Traumatic brain injury TBI
Treatment-resistant depression TRD
Vagus nerve stimulation VNS
Vagus nerve VN

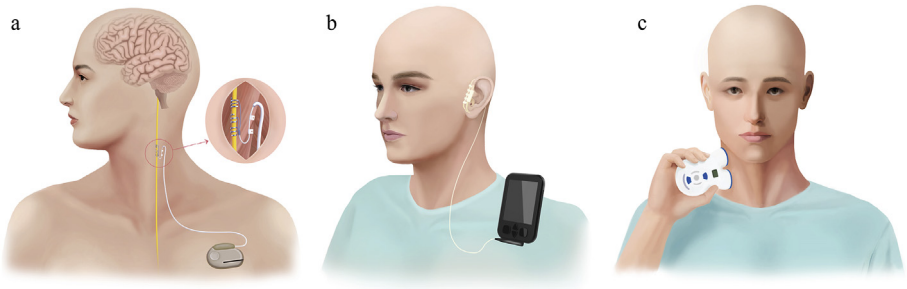

Fig. 1. Devices for vagus nerve stimulation (VNS). (a) Implantable VNS. (b) Transcutaneous auricular vagus nerve stimulation (taVNS). (c) Transcutaneous cervical vagus nerve stimulation (tcVNS).

should be thoroughly studied for the treatment of ischemic stroke.

The Food and Drug Administration (FDA) has approved the therapeutic use of implantable VNS devices (Fig. 1a) in patients with medically refractory, partial-onset seizures (Panebianco et al., 2015; Ben-Menachem et al., 2013) and treatment-resistant depression (TRD) (Conway and Xiong, 2018; Conway et al., 2018). In 2017, transcutaneous cervical vagus nerve stimulation (tcVNS) (Fig. 1c) received FDA approval for the treatment of migraine (Tassorelli et al., 2018) and cluster headache (Redgrave et al., 2018a). Additionally, emerging research is expanding the potential use of VNS to a wider range of therapeutic applications in other neurological disorders such as traumatic brain injury (TBI) (Zhou et al., 2014; Pruitt et al., 2016), intracerebral hemorrhage (Welling et al., 2016; Hays et al., 2014a), chronic tinnitus (Tyler et al., 2017), Alzheimer's disease (AD) (Sjögren et al., 2002; Merrill et al., 2006), Parkinson's disease (Farrand et al., 2017), and even ischemic stroke (Table 1).

In this review, we begin by providing an overview of the evidence investigating the diverse effects of VNS after stroke, and then thoroughly discuss the potential mechanisms by which VNS could provide neuroprotection and improve neuroplasticity. We also outline the applications of the recently emerging non-invasive VNS (nVNS), especially tcVNS and transcutaneous auricular vagus nerve stimulation (taVNS). Finally, we summarize the advantages and pitfalls of the current applications of VNS and future challenges in its clinical implementation.

2. Effects of VNS on ischemic stroke

In experimental stroke models, VNS has been reported to attenuate cerebral infarct volume, reduce neurological deficits, improve forelimb function, and enhance memory and cognition.

2.1. Reducing infarct size and neurological deficits

Numerous animal experiments (Ay et al., 2009, 2015; 2016; Sun et al., 2012) have demonstrated that VNS reduces infarct size and improves the functional scores of rats with focal cerebral ischemia. Moreover, even a brief period of VNS early in ischemia provided positive effects that lasted for at least three weeks (Hiraki et al., 2012) in rats with cerebral ischemia.

These preclinical findings suggest that VNS bears the promise of improving the outcomes of patients with ischemic stroke from the short term to the long term. These findings also support the hypothesis that VNS not only reduces the extent of brain parenchyma injury via neuroprotective effects in the early period of ischemic stroke, but also alleviates neurofunctional deficits via enhanced neuroplasticity in the chronic rehabilitation period. We will discuss these potential mechanisms in detail.

Besides the independent application of VNS as a stroke treatment, recent studies in animal models indicated that VNS paired with

Table 1
The application range of VNS.

Current clinical use of VNS approved by the FDA
Medically refractory partial-onset seizures
Treatment-resistant depression
Migraine
Cluster headache
Potential uses of VNS
Traumatic brain injury
Intracerebral hemorrhage
Chronic tinnitus
Alzheimer's disease
Parkinson's disease
Ischemic stroke

rehabilitative training can enhance neural plasticity in the primary sensory and motor cortices, and improve forelimb strength (Khodaparast et al., 2013, 2016; Hays et al., 2016, 2014b) in rats with cerebral infarction. Some pilot studies (Dawson et al., 2016; Redgrave et al., 2018b; Capone et al., 2017) with small sample sizes suggest that VNS paired with rehabilitation is a promising approach to improve limb motor scores in chronic stroke patients. In addition, another study showed that VNS paired with tactile training improved sensory function in one patient (Kilgard et al., 2018).

2.2. Improving memory and cognition

VNS may also be a useful candidate for the treatment of ischemic stroke patients with memory and cognitive deficiencies. One study showed that VNS improved cognitive functioning and induced spatial and fear memory recovery after cerebral ischemia/reperfusion (I/R) injury in rats (Liu et al., 2016). It has been hypothesized that VNS triggers the release of norepinephrine (NE) in the hippocampus and infralimbic cortex through the locus coeruleus (LC) nucleus. Increased extracellular NE concentrations contributed to the effects of VNS on learning and memory, mood, and recovery of function following cerebral ischemic injury. In this particular study, VNS was applied 30 min before and after ischemia as a single protocol. Additionally, VNS in conjunction with rehabilitation has emerged as a potential therapy to improve memory. For example, VNS paired with a tone was found to enhance memory and cortical plasticity in rats (Loerwald et al., 2018). VNS paired with training enhanced memory retention in rats (Clark et al., 1998) and humans (Clark et al., 1999). VNS has also been reported to improve memory and cognition in patients with AD (Vonck et al., 2014), epilepsy (Sun et al., 2017; Stefan et al., 2012), depression (Desbeaumes Jodoin et al., 2018), cerebral palsy (Jaseja, 2008). An open-label pilot study (Sjögren et al., 2002) suggested a positive effect of VNS on cognition in patients with AD, supporting the long-term tolerability of VNS (tested up to one year) in patients (Merrill et al., 2006).

The precise mechanism by which VNS induces cognitive improvement has not been investigated in-depth and remains elusive; however, the thalamocortical system (Shiramatsu et al., 2016) and the medial reticular formations of the medulla (Ogbonnaya and Kaliaperumal, 2013) may mediate this process.

3. Anatomical basis of VNS

The VN, the longest and most widely distributed cranial nerve, is composed of 80% afferent nerve fibers. Most of the afferent branches of the VN project to the nucleus tractus solitarious (NTS) of the bilateral medulla oblongata (Cheyuo et al., 2011). The NTS is involved in processing and integrating large amounts of visceral and somatosensory information (Bailey et al., 2008). Through the NTS, the VN sends extensive projections to different brain regions such as the cortex, hippocampus, thalamus, and the forebrain's cholinergic system (Cheyuo et al., 2011).

The NTS mainly provides input to the LC, which is the main source of NE in the brain, especially in the cerebral cortex (Zec and Kinney, 2003). The NTS also activates the dorsal raphe nucleus (DRN), which triggers serotonin release from a wide range of brain regions including cerebral cortical serotonergic neurons.

The activation of the VN is involved in multiple brain functions that can, therefore, be potentially modulated by VNS. It was reported that VNS activated NE and serotonergic neurons (Manta et al., 2009) and increased the extracellular concentration of NE in the hippocampus and cortex of rats (Roosevelt et al., 2006). NE and serotonin play a critical role in many cerebral physiological and pathological processes. NE was shown to provide neuroprotection by reducing oxidative stress (Jhang et al., 2014), provide neurotrophic support to neurons (Counts and Mufson, 2010), inhibit glutamate release (Florin-Lechner et al., 1996), restrict the development of neuroinflammatory activation (Feinstein et al., 2016), and sustain hippocampal neurogenesis (Coradazzi et al., 2016). Serotonin was found to suppress excitotoxicity (Marcoli et al., 2004) and regulate adult hippocampal neurogenesis (Alenina and Klempin, 2015).

The efferent vagal fibers exit the skull and then become part of nerve bundles such as the plexus pulmonalis, plexus cardiacus, and plexus coeliacus. They regulate the important physiological functions of the peripheral organs such as the heart, intestine, and spleen.

4. Potential mechanisms of VNS in ischemic stroke

Although the mechanism of action of VNS remains to be determined, some possibilities have been eliminated. The sphenopalatine ganglion (SPG), which is connected to the NTS through the superior salivatory nucleus, provides innervation to the major cerebral blood vessels (Hara et al., 1993). However, the mechanisms of VNS in ischemic stroke may not include alterations in cerebral blood flow (Sun et al., 2012; Ay et al., 2011) and SPG projections (Ay and Ay, 2013). Stimulation of both the right and left VN has comparable effects, and VNS is effective after both ipsilateral and contralateral focal ischemia (Ay et al., 2011).

Recovery from ischemic stroke can be summarized to be generated via two main mechanisms: 1) neuroprotection in the early stage of focal ischemia to minimize neuron death in the ischemic penumbra, and 2) neuroplasticity in a relatively late phase of stroke to maximize the recovery from ischemic injury. This classification is not absolute but helps provide a simple and clear understanding of the underlying mechanisms of VNS in different phases of ischemic stroke.

Neuroprotection may be beneficial to improve the capacity of neural cells to withstand cerebral ischemia. Potential neuroprotection therapies aim to interrupt or reverse adverse events such as excitotoxicity, oxidative stress, inflammatory reaction (Chamorro et al., 2016), apoptosis, and mitochondrial dysfunction. Stroke also results in damage to the neurovascular unit and consequent impairment of synaptic connections and neuronal processes. The possible mechanisms of VNS induced neuroplasticity in ischemic stroke may range from activity-depending rewiring, and the strengthening of synapses, to the production of new neurons and blood vessels (Murphy and Corbett, 2009).

4.1. Inhibiting oxidative stress and reducing excitotoxicity

The imbalance between the cellular production of free radicals and the ability of cells to defend against it is referred to as oxidative stress (OS). OS is one of the pathological mechanisms contributing to neuronal damage after cerebral I/R (Radak et al., 2014). Excessive glutamate release after ischemia is regarded as an important factor in ischemic brain damage as it leads to the generation of free radicals or reactive oxygen species (ROS).

It was confirmed in a rat model of cerebral I/R that VNS regulates malondialdehyde, glutathione, and superoxide dismutase levels in cortical and subcortical (Ekici et al., 2013) brain regions and inhibits the celluar responses to OS, which is possibly associated with increased microRNA-210 expression (Jiang et al., 2015b). The neuroprotective and antioxidant properties of VNS support its efficacy as a potential anti-ischemic treatment. VNS was also found to decrease brain OS in insulin-resistant rats (Chunchai et al., 2016; Samniang et al., 2016), which could attenuate cognitive decline. Moreover, VNS alleviated myocardial injury, preserved antioxidant enzyme activity, and inhibited the formation of ROS and OS after myocardial ischemia (Kong et al., 2012; Chen et al., 2016; Nuntaphum et al., 2018).

There is also evidence that VNS suppresses excitotoxicity in animal models of cerebral ischemic stroke; specifically, VNS significantly attenuated both ischemia-induced glutamate excitotoxicity and the excessive increase of hippocampal blood flow during reperfusion, ultimately rescuing neurons in the gerbil hippocampus (Miyamoto et al.,

2003) after transient ischemia.

4.2. Anti-inflammatory characteristics

Although the neuroprotective effects of VNS on the ischemic brain are still far from being fully understood, its anti-inflammatory property is considered one of the most likely mechanism occurring shortly after cerebral ischemic injury. Recent studies revealed that VNS could potentially modulate inflammation via a broad vagal neural network (Yuan and Silberstein, 2016a). VNS may exert a neuromodulatory effect to activate certain innate, protective pathways in the central nervous system (CNS).

The cholinergic anti-inflammatory pathway (CAIP) describes a physiological mechanism by which the CNS regulates immune responses via the VN and is currently considered to play a crucial role in the process of modulating neuroinflammation after ischemic stroke (Han et al., 2017; Hoover, 2017; Duris et al., 2017; Fu et al., 2017). When CAIP is activated by VNS after cerebral ischemia, efferent vagus signals induce splenic nerves to release NE and activate T cells. Then, acetylcholine generated from these T cells acts on α7 nicotinic acetylcholine receptors (α7 nAChR), which are mainly expressed on macrophages. Ultimately, the complete pathway suppresses the release of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) (Bernik et al., 2002; Bonaz et al., 2013) from being released into circulation (Fig. 2). The spleen is an important peripheral relay station for CAIP. Accordingly, it was found that the protective effects of VNS were abolished in animals after splenectomy (Inoue et al., 2016). Targeting the CAIP with VNS under the condition of ischemic or hemorrhagic stroke is a promising method of immunomodulation that indirectly attenuates neuroinflammation without causing immunosuppression (Duris et al., 2017).

The α7 nAChR has been identified as the central target of VNS in its anti-inflammatory pathway in ischemic stroke (Hoover, 2017). Lu's results suggested that the VNS-induced neuroprotective effects on cerebral infarcts may be related to suppressed inflammation via activation of the α7 nAchR anti-inflammatory pathway (Lu et al., 2017b). The CAIP maintains the homeostasis of the CNS and responds to acute ischemic injury, and rapid nerve conduction can provide instantaneous input for modulating inflammation (Inoue et al., 2016). Therapeutic VNS was shown to activate both efferent and afferent fibers and suppress systemic inflammation via the selective activation of afferent fibers in the abdominal vagus (Komegae et al., 2018), which supports a neural circuit of inflammatory modulation (Johnson and Wilson, 2018).

Jiang's studies indicated that VNS was neuroprotective in acute cerebral I/R injury by suppressing neuroinflammation (Jiang et al., 2014). In addition, VNS upregulated the expression of peroxisome proliferator-activated receptor γ (PPARγ) in the ischemic penumbra, diminished the extent of the ischemic infarct, alleviated neuronal injury, suppressed the expression of pro-inflammatory cytokine TNF-α and interleukin (IL) 1β, and triggered the activation of immune cells. Therefore, PPARγ may participate in the process by which VNS modulates the neuroinflammatory response following cerebral I/R in rats (Jiang et al., 2015a), which is partly via activation of cholinergic and α7 nAchR pathways.

VNS was also proven to play a protective role in ischemic models of other organs. For example, VNS decreased the release of proinflammatory molecules and attenuated kidney I/R injury in mice through α7 nAChR-positive splenocytes (Inoue et al., 2016; Atkinson, 2016). VNS reduced cardiac infarct size and inhibited TNF-α mediated inflammatory response pathways in rat models of acute myocardial infarction (Kong et al., 2011; Kiss et al., 2017), which was probably mediated via α7 nAchR and CAIP (Wang et al., 2003; Borovikova et al., 2000). In addition, VNS suppressed neuroinflammation and OS (Chen et al., 2018), which alleviated cerebrocortical micro infarcts.

In parallel, accumulating evidence shows the protective role of VNS via the regulation of inflammatory responses in many other pathological conditions such as intestinal inflammation (Langness et al., 2017; Jin et al., 2017; Meroni et al., 2018; Sun et al., 2013), TBI (Neren et al., 2016; Bansal et al., 2012), chronic pain (Chakravarthy et al., 2015), heatstroke (Yamakawa et al., 2013), atrial fibrillation (Qian et al., 2018), heart failure (Zhang et al., 2009), aortic occlusion (Bernik et al., 2002), severe rheumatoid arthritis disease (Koopman et al., 2017), obesity-associated insulin-resistance (Samniang et al., 2016), refractory epilepsy (Majoie et al., 2011), cardiopulmonary resuscitation (Sun et al., 2018), developing brainstem (Johnson et al., 2016), and lipopolysaccharide-induced neuroinflammation (Meneses et al., 2016). These findings support the generalizability and potential efficacy of the anti-inflammation effects of VNS on ischemic stroke.

4.3. Protecting the blood-brain barrier and attenuating brain edema

The integrity of the blood-brain barrier (BBB) plays a vital role in regulating the trafficking of fluid, solutes, and cells at the blood-brain interface and maintaining the homeostatic microenvironment of the CNS under physiological and pathological conditions such as ischemic stroke (Jiang et al., 2018).

tcVNS significantly decreased the BBB transfer rate in the lesion area and lowered serum IgG leakage in a rat model of ischemic stroke 24 h after the injury, which was spatially correlated with the attenuation of the cerebral infarct size. It also protected vascular tight junction proteins from disruption in microvessels and reduced the expression of matrix metalloproteinases-2/9 in reactive astrocytes surrounding the compromised vessels (Yang et al., 2018). It was also proved using two-photon imaging that VNS improved the BBB integrity (Chen et al., 2018) after cerebral cortical micro infarcts. Additionally, VNS protected BBB integrity and attenuated symptoms in rat models of other pathological conditions, such as cortical dysplasia (Kaya et al., 2013) and TBI (Lopez et al., 2012), which could also contribute to understanding VNS effects on the BBB after ischemic stroke.

Disruption of the BBB and extravasations of serum proteins result in vasogenic brain edema (Michinaga and Koyama, 2015). Taking into account that VNS-mediated attenuation of cerebral edema (Clough et al., 2007; Lopez et al., 2012; Neren et al., 2016; Kumaria and Tolias, 2012) has been demonstrated in rats subjected to TBI, it would not be surprising that the VN may play an important role in regulating cerebral edema after ischemic stroke (Cai et al., 2014).

4.4. Suppressing cell apoptosis

Apoptosis may contribute to significant neuronal death following acute cerebral ischemia (Radak et al., 2017). The potential anti-apoptotic property of VNS may be one of the mechanisms underlying its neuroprotective role in ischemic stroke.

Recent studies indicated that VNS significantly decreased the number of TdT mediated dUTP nick end labeling positive cells and cleaved caspase 3 protein in the ischemic penumbra of rats subjected to acute cerebral I/R injury, indicating that the neuroprotection of VNS is partly via inhibition of neural apoptosis (Jiang et al., 2014, 2015b). Furthermore, VNS decreased neuronal apoptosis after cerebral I/R injury (Zhang et al., 2016) by downregulating Bax and cleaved caspase-3 as well as upregulating Bcl-2, which is possibly mediated by lipocalin prostaglandin D2 synthase. Another study found that VNS decreased

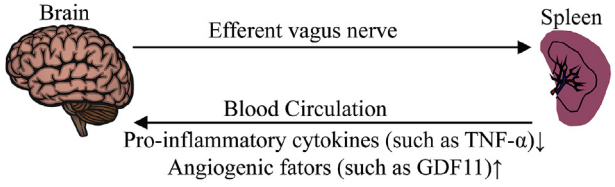

Fig. 2. VNS mediated brain-spleen communication after cerebral ischemia.

the expression of apoptosis-associated proteins and reduced myocardial apoptosis by downregulating microRNA-215 in rats with chronic heart failure (Xuan et al., 2017). VNS also significantly suppressed cardiomyocyte apoptosis (Nuntaphum et al., 2018; Chen et al., 2016; Xue et al., 2017) in models of myocardial ischemia.

4.5. Ameliorating mitochondrial dysfunction

Mitochondrial dysfunction is regarded as one of the hallmarks of cerebral I/R injury induced neuronal death. Accordingly, maintaining the function of mitochondria is crucial in promoting neuron survival and neurological improvement (Liu et al., 2018).

Some studies provide evidence of a mitochondria-dependent mechanism of VNS. For example, VNS significantly attenuated mitochondrial dysfunction (Nuntaphum et al., 2018; M. Chen et al., 2016; Shinlapawittayatorn et al., 2013, 2014) after a myocardial I/R injury. Besides, VNS modulated mitochondrial dynamics, enhanced adenosine triphosphate (ATP) content, stabilized mitochondrial membrane potential, reduced the mitochondrial permeability transition pore opening, and improved mitochondrial ultrastructure and size, ultimately enhancing mitochondrial function to attenuate myocardial ischemia (Xue et al., 2017). It was also demonstrated that VNS protected mice with a burn injury from further cardiac injury by attenuating mitochondrial dysfunction (Lu et al., 2013). Specifically, VNS suppressed cardiomyocyte apoptosis, decreased mitochondrial swelling and myocardial ATP content, and regulated apoptotic signaling pathways. These independent findings support the idea that targeting mitochondrial dynamics with VNS may provide a novel therapeutic strategy in acute ischemic diseases.

4.6. Enhancing neuronal plasticity

The plasticity-enhancing role of VNS has been demonstrated in some animal studies. For example, Biggio et al. (2009) found that VNS induced the proliferation of hippocampal dentate gyrus neurons, enhanced persistent neuronal plasticity, and increased the expression of brain-derived neurotrophic factor (BDNF) in the rat hippocampus, all of which indicate a potential role in the therapeutic efficacy of VNS in ischemic stroke. Meyers et al. (2018) discovered that VNS enhanced plasticity in corticospinal motor networks to increase synaptic connectivity to the musculature of the rehabilitated forelimb in rats subjected to unilateral cortical and subcortical ischemia, and that the improvements lasted months after the end of VNS. Furthermore, Zuo et al. (2007) findings suggested that VNS may affect memory processes by modulating neural plasticity in the hippocampus of freely-moving rats.

The brain reveals a spectrum of intrinsic capacities to react as a highly dynamic system that can change the properties of its neural circuits. This brain plasticity can lead to an extreme degree of spontaneous recovery, and therefore, interventions targeting neuronal plasticity could accelerate rehabilitation after stroke (Hara, 2015). As mentioned before, recent animal studies have demonstrated that VNS paired with physical training can enhance movement-specific plasticity within the motor cortex (Porter et al., 2012; Khodaparast et al., 2013) and improve forelimb function after stroke (Khodaparast et al., 2013, 2016; Hays et al., 2014b, 2016).

Targeted plasticity-enhancing therapies utilizing VNS can provide the specificity required to restore normal neural activity in those dysfunctional neural circuits that are assumed to underlie many neurological diseases (Hays et al., 2013). Recent studies also support the hypothesis that pairing sound with VNS can direct therapeutic neural plasticity in rats (Loerwald et al., 2018) as well as patients with tinnitus (Vanneste et al., 2017; Engineer et al., 2013). Moreover, VNS was reported to increase neural plasticity that underlies recovery of function in rats with intracerebral hemorrhage (Hays et al., 2014a), TBI (Smith et al., 2005), and insulin-resistance (Chunchai et al., 2016). These results support the idea that VNS can enhance the neural plasticity, which is the basis of motor and cognitive recovery from ischemic injury.

4.7. Stimulating neurogenesis

After ischemic stroke, endogenous adult cerebral neurogenesis, mainly occurs in the subventricular zone, along the walls of the lateral ventricle, and in the subgranular zone of the dentate gyrus (DG), which contribute to neurovascular repair and functional recovery from ischemic injury (Lu et al., 2017a).

It was suggested that VNS induced an increase in the number of available progenitor cells in the adult rat DG by a mechanism involving increased hippocampal progenitor cell proliferation (Revesz et al., 2008; Ogbonnaya and Kaliaperumal, 2013), which supports the notion that VNS-induced hippocampal plasticity is involved in its efficacy in treating ischemic stroke. Another study demonstrated that VNS ameliorated behavioral deficits and stimulated hippocampal neurogenesis in a rat model of depression (Gebhardt et al., 2013). A recent study showed that 6 and 12 months of treatment with VNS could significantly and progressively increase hippocampal gray matter volumes in TRD patients, which suggests a modulatory effect of VNS on hippocampal plasticity (Perini et al., 2017). It was also speculated that VNS may play a role in upregulating endogenous neurogenesis after TBI (Kumaria and Tolias, 2012; Neren et al., 2016). It is therefore possible that VNS-mediated upregulation of neurogenesis contributes to improved recovery following cerebral ischemia.

None of the research findings to provide direct evidence for the role of VNS in post-stroke neurogenesis, and more work using experimental stroke models is needed to fully elucidate this mechanism of action.

4.8. Inducing angiogenesis

There is growing evidence to suggest that the surge of cerebral angiogenesis (Liu et al., 2014) after stroke causes the increase in cerebral blood volume observed during the late phase of stroke, which plays an important role in the recovery of neural function in human stroke patients (Krupinski et al., 1994).

Recent studies discovered that taVNS enhanced the expression of angiogenic factors such as BDNF, endothelial nitric oxide synthase, and vascular endothelial growth factor, induced proliferation of endothelial cells, stimulated angiogenesis, and increased microvessel density surrounding the infarct area in cerebral I/R rats (Jiang et al., 2016; Ma et al., 2016), in addition to ameliorating neural symptoms and decreased infarct volume.

In our previous studies, we found that growth differentiation factor 11 (GDF11) stimulated angiogenesis in rats subjected to cerebral I/R (Ma et al., 2018). taVNS improved post-stroke recovery, upregulated cerebral GDF11, and downregulated splenic GDF11 (Ma et al., 2016), indicating brain-spleen communication during stroke. When ischemic signals were released from the brain after stroke, VNS treatment mediated the brain-spleen communication via the efferent VN. Then, the activated spleen mobilized its GDF11 reserves into the blood circulation, which allowed its subsequent accumulation in the ischemic brain (Fig. 2).

VNS was also reported to promote angiogenesis/arteriogenesis in repairing the infarcted heart (Lv et al., 2018). Moreover, studies investigating VNS revealed a potential role in protecting vascular endothelial cells and regulating the vasculature in rat models of myocardial I/R (Zhao et al., 2013), heatstroke (Yamakawa et al., 2013), severe hypertension (Chapleau et al., 2016), female menopause (Li et al., 2016), and endotoxemia (Mihaylova et al., 2012). These findings represent a significant understanding of the potential role of VNS in vascular protection after ischemic stroke.

5. Adverse effects of VNS

The complications of VNS therapy arise early (related to surgery)

and late (related to the device and to stimulation of the VN) (Giordano et al., 2017) in the application process. Early complications include intraoperative bradycardia and asystole, peritracheal hematoma, infections (3–8%), and VN injury followed by hoarseness, dyspnea, and dysphagia. Late complications due to nerve stimulation include delayed arrhythmias, laryngopharyngeal dysfunction, obstructive sleep apnea, stimulation of the phrenic nerve, tonsillar pain mimicking glossopharyngeal neuralgia, and vocal cord damage. In general, the adverse effects of VNS are generally of mild-to-medium severity, and most of the problems can be easily eliminated by re-adjusting of the stimulator without removal of the device (Ekmekçi and Kaptan, 2017).

Some clinical pilot studies (Dawson et al., 2016; Redgrave et al., 2018b; Capone et al., 2017) have demonstrated that VNS paired with rehabilitation is feasible and effective in adults with chronic stroke. In addition, VNS is likely well-tolerated in patients with comorbidities such as dementia and heart diseases as VNS does not cause cognitive or systemic adverse effects. VNS is also feasible and safe in chronic-stage ischemic stroke patients as it is suitable for long-term administration (Dawson et al., 2016). It is encouraging that chronic VNS is feasible and well-tolerated even in patients with heart failure and reduced ejection fraction (Premchand et al., 2014). The improvement of disease symptoms after VNS therapy was maintained for up to 12 months (Premchand et al., 2016).

6. Non-invasive VNS

Classical VNS directly stimulates the VN in the neck via surgically implanted electrodes and a stimulator (Fig. 1a). Although it has been shown to be effective in reducing infarct volume in rats, it is not feasible in the context of acute human stroke as it requires a surgical incision in the neck. Newer nVNS delivery systems, which do not require a surgical procedure, may be a better choice for an emergency patient with bursts of ischemic stroke. nVNS is safe and well-tolerated at the doses tested to date, and serious adverse events are very rare (Redgrave et al., 2018a). The specific anatomical placement of the nVNS device (Fig. 1b and c) varied by study; those using tcVNS stimulated the VN at the cervical region (a cervical branch of the VN) and those using taVNS stimulated at the external ear (an auricular branch of the VN) (Redgrave et al., 2018a; Yuan and Silberstein, 2016b).

Ay's group presented a novel perspective on the role of VNS in ischemic stroke with tcVNS (Ay et al., 2016) and taVNS (Ay et al., 2015), both of which had significant neuroprotective effects and decreased the infarct volume in rats with cerebral ischemia. For tcVNS, the study specifically developed an experimental, non-invasive stimulator. Surface electrodes were placed on the neck skin overlying the cervical VN, without applying any extra mechanical pressure. This indirect stimulation inhibited ischemia-induced immune activation and reduced the extent of tissue injury and functional deficit in rats with acute ischemic injury without causing cardiac or hemodynamic adverse effects (Ay et al., 2016). Furthermore, Nonis' study provided electrophysiological evidence of tcVNS in healthy volunteers, in whom tcVNS activated afferent fibers of the VN by eliciting vagal somatosensory evoked potentials (Nonis et al., 2017). tcVNS was found to regulate cerebral ischemia-related inflammatory processes by promoting microglial M2 polarization (Zhao et al., 2019). These findings raise the possibility that tcVNS may be a viable substitute for implantable VNS.

taVNS has been proven to activate brainstem afferent vagal nuclei in rats with acute ischemic stroke (Ay et al., 2015), similar to implantable VNS. The target of taVNS is the auricular branch of the vagal nerve (ABVN), a unique cutaneous subdivision of the vagus distributed to the external ear (Murray et al., 2016). A study using functional magnetic resonance imaging (fMRI) demonstrated that the most effective and optimal location for taVNS therapies applied to the auricle is at the cymba concha (Yakunina et al., 2017). Frangos' findings provided anatomical fMRI evidence of taVNS in humans; the projections of the ABVN to the NTS were found to be consistent with the "classical" central vagal projections and can be accessed non-invasively via the external ear (Frangos et al., 2015). In addition, taVNS significantly reduced sympathetic nerve activity in healthy participants (Clancy et al., 2014). These results indicated that nVNS may share the same pathway or mechanism as classical VNS.

Stimulating certain areas of the ear in the treatment of stroke is not a new concept. Acupuncture, a traditional Chinese therapeutic method, has a long history of applying aural stimulation to achieve recovery from stroke. Auricular acupuncture and taVNS may accomplish the same or similar treatment procedure despite being guided by different theoretical ideas (Kong et al., 2018); auricular acupuncture points used in the treatment of pain are situated in areas innervated mostly by the ABVN (Usichenko et al., 2017). It was also demonstrated that electroacupuncture stimulation of the auricular concha shares a CAIP mechanism with VNS (Zhao et al., 2011).

Due to its non-invasive nature, taVNS is a simple, portable, cost-effective, and patient-targeted strategy, which makes it more translatable across a wide range of uses (Ben-Menachem et al., 2015). Overall, two important potential advantages of the clinical translation of taVNS should be highlighted: (1) taVNS can be easily integrated with thrombolysis and antiplatelet therapy as a feasible adjunctive treatment in ischemic stroke, in the acute phase (in the ambulance) and as a secondary prophylactic option during the chronic phase (Ay et al., 2015). taVNS has already been determined to be feasible and well-tolerated in patients in the chronic phase of stroke recovery (Redgrave et al., 2018b). Though animal studies have suggested the use of VNS in the early stage of stroke, its application in the acute or superacute phase post-stroke still needs verification in the clinical setting. (2) Since taVNS was found to be feasible in both ischemic and hemorrhagic stroke patients (Capone et al., 2017), it holds promise as an acute clinical therapy (in the ambulance or the patients' home) that can be provided without the skull computed tomography scan to determine whether the stroke event is ischemic or hemorrhagic. It can be a beneficial complementary strategy before the "Stroke Unit" (Jung et al., 2015).

7. Current challenges

With the recent development of implantable and portable VN stimulators, growing evidence suggests that VNS can be used for treatment of stroke patients; however, this treatment option still faces huge challenges before moving from preclinical research to clinical application in humans. Below, we have discussed four aspects of the challenges facing VNS as a clinical treatment for ischemic stroke.

7.1. Stimulation parameters

Setting the ideal stimulation parameters for VNS is one of the most critical challenges facing its application, as these parameters have huge impacts on clinical efficacy. For example, the plasticity-enhancing and memory-enhancing effects of VNS follow an inverted-U pattern of stimulation current to response, which is influenced by pulse width. Shorter pulse widths may offer a clinical advantage when determining optimal stimulation current (Loerwald et al., 2018). Similarly, stimulation intensity also influences motor cortex plasticity (Morrison et al., 2019). In fact, there are numerous parameters such as stimulation sites and sides, electrode and waveform configuration, efferent or afferent stimulation, continuous stimulation or pulse-synchronous stimulation, frequency and amplitude of current, titration protocols, and maximum current, and stimulation on-and-off time that may affect the clinical efficacy of VNS (De Ferrari and Schwartz, 2011). Therefore, the effectors of stimulation parameters and the resultant direction of the cognitive effects of VNS seem to depend strongly on stimulation conditions (Helmstaedter et al., 2001). In addition, the timing of VNS initiation (Shinlapawittayatorn et al., 2014; Hays et al., 2014b) and the amount (Hays et al., 2014b) of its use also play key roles in maximizing its

Table 2
Stimulation parameters and effects of VNS.

Author & year	Rats/ human	Device	Pulse width	Frequency	Intensity	Stimulation train	Stimulation interval	Stimulation duration	Effects of VNS on IS
Ay et al. (2009)	Rats	Implantable VNS	0.5 ms	20 HZ	0.5 mA	30 s	Every 5 min/30 min	1 h/3 h	Reduces infarct size and improves functional score
Sun et al. (2012)	Rats	Implantable VNS	0.3 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Reduces infarct size
Hiraki et al. (2012)	Rats	Implantable VNS	0.3 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Reduce infarct size, improves chronic outcome
Ekici et al. (2013)	Rats	Implantable VNS	0.5 ms	20 HZ	1 mA	30 s	12 s off	–	Reduce infarct size, improves functional score and inhibites oxidative stress
Khodaparast et al. (2013)	Rats	Implantable VNS	0.1 ms	30 HZ	0.8 mA	500 ms	15 pulses	25 d	VNS paired with rehabilitation restores forelimb function
Jiang et al. (2014)	Rats	Implantable VNS	0.5 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Suppresses inflammation
Jiang et al. (2015b)	Rats	Implantable VNS	0.5 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Inhibites oxidative stress and apoptosis
Hays et al. (2016)	Rats	Implantable VNS	0.1 ms	30 HZ	0.8 mA	500 ms	15 pulses	5 w	VNS paired with rehabilitation restores forelimb function
Liu et al. (2016)	Rats	Implantable VNS	0.4 ms	20 HZ	1 mA	3 s	3 s interval	10 min	Improves cognitive function
Zhang et al. (2016)	Rats	Implantable VNS	0.5 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Inhibites apoptosis and protects against I/R injury
Lu et al. (2017b)	Rats	Implantable VNS	0.5 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Suppresses inflammation
Meyers et al. (2018)	Rats	Implantable VNS	0.1 ms	30 HZ	0.8 mA	500 ms	15 pulses	–	VNS paired with rehabilitation enhances plasticity
Ay et al. (2015)	Rats	taVNS	0.5 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Reduces infarct size and activates afferent vagal nuclei
Ma et al. (2016)	Rats	taVNS	0.5 ms	20 HZ	0.5 mA	30 s	Every 5 min	1 h	Induces angiogenesis
Ay et al. (2016)	Rats	tcVNS	1 ms	25 HZ	12 V sine waves	2 min	Every 10 min	1 h	Reduces tissue injury and inhibits microglia activation
Yang et al. (2018)	Rats	tcVNS	1 ms	25 HZ	15 V sine waves	2 min	Every 10 min	1 h	Protects the BBB
Zhao et al. (2019)	Rats	tcVNS	1 ms	25 HZ	15 V sine waves	2 min	Every 10 min	1 h	Protects against I/R injury and promotes microglial M2 polarization
Dawson et al. (2016)	Human	Implantable VNS	0.1 ms	30 HZ	0.8 mA	500 ms	15 pulses	–	VNS paired with rehabilitation is feasible
Capone et al. (2017)	Human	taVNS	0.3 ms	20 HZ	Individual adjust	30 s	Every 5 min	1 h	VNS paired with rehabilitation improves upper limb function
Kilgard et al. (2018)	Human	Implantable VNS	0.1 ms	30 HZ	0.8 mA	500 ms	–	–	VNS paired with tactile training improves sensory function
Redgrave et al. (2018b)	Human	taVNS	0.1 ms	25 HZ	Maximum tolerance	–	–	1 h	VNS paired with rehabilitation is feasible

therapeutic benefits.

Here, we have listed the detailed stimulation parameters of VNS in some studies (Table 2). In animal studies, the stimulation intensity ranges from 0.5 to 1 mA. A human study slowly increased stimulation intensity by 0.1 mA increments until the maximum tolerable level reported by participants (Redgrave et al., 2018b). Another study individually adjusted the stimulation intensity to a level ranging above the detection threshold and below the pain threshold (Capone et al., 2017). Although these animal and human trials of VNS have shown promising results with minimal adverse events, further research intensively comparing a larger range of stimulation conditions to maximize the treatment effects of VNS (Mertens et al., 2018; Kong et al., 2018) is still necessary.

7.2. Difference between animal models and the human condition

The translatability of any medical treatment to humans is a well-known challenge in biomedical research. A relevant example exists in the case of VNS; while investigations in animal models have successfully resulted in a reduction of inflammation, the anti-inflammatory effects of VNS are not supported by clinical studies in patients with refractory epilepsy (Barone et al., 2007) and endotoxemia (Kox et al., 2015). This difference is likely because rodent models may not be good predictors of VNS treatment effects in humans (Kwan et al., 2016). The clinical translation of VNS from animal model to human is questionable (Cai et al., 2014) due to the anatomical and physiological differences between rats and humans.

Although the mechanisms responsible for VNS treatment efficacy are now better understood thanks to studies in experimental stroke models, VNS still lacks success in large clinical trials as an independently administered therapy in stroke patients.

7.3. Limiting factors

There are some other important factors that could limit the clinical effects of VNS (Hays, 2016). These factors include the advanced age of some patients, other common pharmaceuticals that target the cholinergic and noradrenergic systems, and comorbidity of stroke with diseases that impair neuromodulatory function. To fully explore the potential application of VNS in humans, such key patient-specific details cannot be neglected.

7.4. Individual patient differences

Lastly, a single VNS protocol cannot be assigned to all patients (De Ferrari and Schwartz, 2011) due to the individual differences between patients. Different patients may respond best to different combinations of parameter settings. Moreover, some patients may fail to respond to any type of VNS. Physicians and researchers have yet to determine which VNS method would best balance practicality and efficacy: unified standard parameters for widespread and commercial use or personalized parameters to serve individual patients.

Since the signaling pathways and mechanisms underlying the efficacy of VNS in ischemic stroke are far from fully understood, it is the responsibility of the physicians and researchers to disclose these individual differences and optimize the diverse parameter settings (Cai et al., 2014) on a case-by-case basis.

8. Future directions

Following the promising preclinical data suggesting that this novel intervention provides positive improvements after ischemic stroke, it would be invaluable to reproduce the beneficial effects of nVNS in patients with ischemic stroke. Further confirmation of the treatment in large, randomized, controlled clinical trials with adequate sample sizes is needed, both for the chronic phase and acute phase of stroke.

VNS paired with rehabilitative training has emerged as a potential, targeted plasticity therapy (Hays, 2016; Hays et al., 2013) to enhance the benefits of rehabilitative stroke interventions. The development of taVNS as an adjunctive strategy that enhances overall plasticity to facilitate the benefits of rehabilitative interventions has the potential to improve recovery from cerebral ischemic injury. Therefore, well-designed prospective studies are strongly recommended to develop applicable technology for the use of VNS alone or in combination with other therapies.

Recently, new devices to non-invasively manipulate VN function have been developed, with the aim of achieving the optimal effects of VNS without its drawbacks (Mertens et al., 2018). It is encouraging that commercialized, stable, human-targeted stimulation devices have emerged to meet the urgent needs of pain control. For example, the NEMOS (Cerbomed, Germany) stimulates the concha of the outer ear and is marked for the European market (Redgrave et al., 2018a) (Fig. 1b). There is also a hand-held stimulation device, GammaCore (Electrocore, USA), that is applied to the neck (Fig. 1c) and is now a FDA-approved treatment for migraine and cluster headache (Simon and Blake, 2017). The latest tcVNS-related treatment option being investigated is an ultrasound-guided stimulation therapy, which is close to a targeted VN stimulation therapy in humans (Huffman et al., 2019). Other novel devices designed for the clinical application of VNS in ischemic stroke should be under development.

In conclusion, although mechanistic and clinical research is still required to fully understand VNS, we are now at the threshold of the clinical use of VNS in the treatment of patients with ischemic stroke.

Conflicts of interest

The authors declare no conflict of interest.

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