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Norepinephrine Might be a New Target on Vagus Nerve

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Opinion

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Abstract

Clinical and experimental studies have shown that vagus nerve stimulation (VNS) provides significant results in neurological diseases such as epilepsy, Parkinson disease, migraine and drug-resistant depression, but its molecular mechanism has not yet fully elucidated. It is known that the therapeutic effect of VNS is caused by the induction of noradrenergic neurons in Locus Coeruleus (LC) and thus increased norepinephrine (NE) release. It has been shown that the effect is achieved by the projections of the vagus nerve extending from the nucleus tract solitarius (NTS) to LC. In this opinion, it was suggested that instead of electrically stimulating the vagus nerve and indirectly increasing NE release, an NE release device that directly targets the NE foci must be developed. In this way, it is thought that the side effects of VNS can be ruled out and a stronger NE response might be obtained at the same time. Therefore, norepinephrine related pathways might be a new target on vagus nerve.

Keywords: Norepinephrine; Experimental Studies; Neurological Diseases; Epilepsy

Introduction

The autonomic nervous system manages the involuntary functions of the body. It is composed of numerous ganglia, plexus, cerebrospinal nuclei and nerve. Autonomic nervous system, sympathetic system, parasympathetic system and enteric system consist of three classes. The main neurotransmitters present in this system are acetylcholine (ACh) and NE. The vagus nerve (10th cranial) is the longest and the only nerve leaving the head of the cranial nerves. It contains both sympathetic and parasympathetic fibers. With the help of these mixed fibers, the vagus nerve stimulates the ACh and NE secretion, and new treatment modalities are being developed against various neurological diseases such as epilepsy, Alzheimer's disease and depression.

VNS is a unique treatment using peripheral intervention to treat a disease related to pathological events in the brain. VNS is currently being used in more than 40,000 patients as an additional treatment for drug-resistant epilepsy. VNS has shown promising results in the treatment of chronic inflammatory disorders such as sepsis, lung injury, rheumatoid arthritis (RA) and diabetes. It is also used in the control of pain in fibromyalgia and migraines.

VNS has been shown to be an approved treatment and therapeutic option for various diseases such as epilepsy,

depression, anxiety, and Alzheimer's disease [1]. Accordingly, the available information for VNS therapy includes modulation of NE release with protrusions extending to the locus coeruleus (LC) affecting the limbic, reticular and autonomic centers of the brain. Further support for the role of noradrenergic neurotransmission comes from a report that suppresses the anti-seizure effects of VNS in animals after LC lesion [2]. It was also showed that VNS causes increased NE in the hippocampus in rodents, which in turn activates LC, a major source of NE in the brain. VNS affects activity in LC and dorsal raphe nuclei (DRN), but the involvement of these neuromodulator networks in VNS-directed plasticity is unknown. In a 2019 study, it was tested that cortical NE is necessary for the development of motor cortex plasticity due to VNS. Noradrenergic depletion inhibited the flexibility of motor representations of the driven cortex by pairing VNS with motor training [3]. These results demonstrate that cortical NE and serotonin are necessary for VNS-mediated plasticity, further demonstrating that NE amounts should be targeted molecularly in neuroplasticity defects such as epilepsy treated with VNS. In another study, transcutaneous vagus nerve stimulation (tVNS) was shown to modulate both the GABAergic and NE system. Stimulation of the vagus nerve in rats increases the concentration of NE. Although both systems are modulated by tVNS, the results show that the modulation of the NE system is crucial for the resulting effects. For example, increased concentrations of NE in the prefrontal cortex have been shown to improve response inhibition performance in patients with attention deficit hyperactivity disorder as studying stop signal and response inhibition processes, such as in rodents and humans. The NE system might also change the effect of work memory load on response prevention processes. Although tVNS leads to a combined modulation of GABAergic and NE system, it is observed that tVNS is the aspect of NE system related to the effects obtained. The effects of NE vary in the prefrontal cortex depending on the type of receptor affected and the site [4].

The effects of VNS on NE concentrations in rat brain were observed. The results showed that acute vagus nerve stimulation increased NE concentration in the prefrontal cortex, similar to the antidepressant drug venlafaxine. These new findings have contributed to the elucidation of the molecular mechanisms underlying the therapeutic effects of VNS using as a treatment modality in neurological diseases [5]. In another study, VNS-induced changes in hippocampal neurotransmitter levels were measured. In conclusion, VNS increased the NE levels in the extracellular hippocampal region [6]. Also, the changes in NE caused by left vagus nerve stimulation at different flow levels were measured. As a result, it was observed that the left VNS produced a concentration-dependent increase in NE concentrations in the hippocampus, and that a 1.0 mA stimulation resulted in a significant increase in NE concentration in the cortex. In addition, the increase in VNS induced NE in both cortex and hippocampus was reported to return to baseline during inters stimulation periods. In the light of all these results, it is considered that a new device targeting NE release should be developed considering the decrease in NE in the inter stimulations period [7].

The NE release device, which is proposed to be developed, is expected to achieve a stronger response by performing chemical stimulation rather than indirect stimulation of the noradrenergic foci in the LC by VNS. However, it is thought that the side effects observed in the periphery with the electrical stimulation of the vagus nerve will not be seen and the treatment rate will reach the maximum level.

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