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REVIEW

THE ROLE OF THE VAGUS NERVE IN DEPRESSIVE DISORDERS: A LITERATURE REVIEW AND THE POTENTIAL OF VAGOTOMY TO CREATE A DEPRESSION PHENOTYPE IN RODENTS

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Abstract. *Major depressive disorder (MDD) affects 280 million people worldwide and is a major global health burden due to its link with suicide, physical comorbidities, and inadequate response to pharmacotherapy in many patients. The monoamine theory of depression has provided therapeutic targets, yet exploring additional mechanisms could enhance therapeutic outcomes and increase remission rates. This review examines the potential role of the vagus nerve in depression. Vagus Nerve Stimulation (VNS) has shown promising results in treating refractory depression and has been FDA-approved for MDD since 2005. Clinical and preclinical evidence suggests that vagotomy or vagus nerve ablation can both induce and alleviate depressive symptoms, depending on the context. Furthermore, we propose that structural and biochemical compromise of the vagus nerve may contribute to affective disorders, including depression, bipolar disorder, and anxiety phenotypes. To test this hypothesis, the intervention in question would involve performing vagotomy in rodents and the subsequent investigation for depression and anxiety phenotypes in the affected animals.*

Key words: *vagotomy, depression, MDD, anxiety, rodents, VNS*

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INTRODUCTION

Major depressive disorder affects more than 280 million people worldwide [5]. Patients suffer from persistent feelings of sadness, hopelessness, loss of interest or pleasure in daily activities, and a variety of physical and cognitive symptoms. Many mechanisms have been hypothesized and some have proven to have a significant impact on the onset and progression of the disorder. In the last few decades, the biochemical action of serotonin has been accepted as a major causative agent of depression [3, 4]. A recent systematic umbrella review from 2022 challenged this dogma, concluding that research on serotonin has not consistently demonstrated a link between serotonin and depression, nor does it support the hypothesis that decreased serotonin activity or levels causes depression [1]. Some findings in the review suggest that prolonged use of antidepressants may even lower serotonin concentrations.

While the following review does not aim to discredit the role of serotonin in depression (on the contrary, the monoamine theory may play a supportive role), it highlights the importance of exploring complementary mechanisms that may contribute to affective disorders. The vagus nerve has emerged as a potential target therapy, and so has the body of evidence

supporting vagus-dependent modulation of mood through the gut-brain axis. Thus, it is of importance to investigate the mechanisms by which the vagus nerve may or may not induce an altered mood.

This review aims to provide insight into the emerging and expanding body of evidence indicating that the vagus nerve plays a significant role in the development of affective disorders, particularly clinical depression. Additionally, it will suggest how this theoretical foundation can be applied to the study of animal models of depression.

EMERGING SUCCESS OF VAGUS NERVE STIMULATION (VNS) AS TREATMENT FOR DEPRESSION

Vagus nerve stimulation (VNS) emerged as a potential treatment after its approval for pharmacoresistant epilepsy in 1997 [1]. Initially, anecdotal observations were made that pointed out that the treated epileptic patients showed improvements in mood. This led to a prospective pilot study that confirmed that VNS patients showed improvement in mood over time in comparison to patients with no intervention and stable AED regimen [7]. The finding was confirmed by a European study (n = 11) which enrolled epileptic patients with mild depression [11].

Initial studies

Later on, a series of pilot studies were conducted with positive results. For example, in a trial of 30 patients with treatment-resistant depression, invasive VNS and following 10-week stimulation led to a response rate of 40 % and a remission rate of 17% [12].

Less convincing results emerged when a controlled pivotal trial (n = 225) of VNS in treatment-resistant depression (TRD) was conducted in which VNS was compared with a sham group and showed a 15% response rate in the VNS group and a 10% response rate in the sham group, which did not show any difference (p = 0.238) [13]. On a more positive note, the one year outcomes showed the response rate remained stable, even increasing from 40% to 46% (p = 0.317), while the remission rate notably improved from 17% to 29% (p = 0.45) after an additional nine months of a long-term vagus nerve stimulation (one year of VNS in total) [14]. Also these studies investigated VNS for patients in which previous treatment had failed which points out that much different response rates might have been encountered in patients with milder forms of depression. Yet so far, invasive VNS procedures are only FDA approved for individuals with severe, pharmacoresistant MDD. Moreover, a combined systematic literature review and meta-analysis published in 2020 in “Comprehensive Psychiatry” included 22 studies that compared VNS with treatment as usual (TAU) and suggests that VNS is a viable option for this population of patients that do not respond to other treatments [8]. A study on rats discovered that locus coeruleus (LC) lesions suppressed the anticonvulsant effect of VNS in the rodents [9]. This finding in combination with the wide knowledge of the role of the LC in affective disorders [10] may help understand the role of the vagus nerve in depression and other affective disorders.

Approval by the Food and Drug Administration (FDA) in 2005

The data leading to the FDA‘s approval of invasive VNS for severe depression included a 2005 randomized controlled trial [29] with 235 patients diagnosed with nonpsychotic affective disorders, both unipolar and bipolar. The enrolled patients had treatment-resistant depression, defined as failure to respond to at least two and up to six drugs. The aim was to test the effect of VNS against the use of a sham procedure for 10 weeks. This study did not result in significant changes and both the VNS group (15%) and the sham group (10%) had some reduction in depressive symptoms measured by the Hamilton Depression Rating Score (HDRS). The failure in significant improvement was explained by underdosing (< 1 mV) and short duration of the procedure, where the authors suggested in retrospect that a treatment duration of at least 3 months was suggested for an appropriate response. A follow-up study of the same patients showed that VNS could also have a cumulative benefit that cannot be accomplished with acute VNS. Response and remission rates at 3, 6, 9 and 12 months were increasingly growing with best results shown after 12 months with reduction rates of 28% (± 5.7 at baseline) and remission rates of 19.6 (± 9.7 at 12 months, p < 0.00) [30].

In 2008 an open, uncontrolled European multicenter study (D03) of VNS therapy was conducted, in addition to stable pharmacotherapy, in 74 patients with TRD. Treatment remained unchanged for the first 3 months; in the subsequent 9 months, medications and VNS dosing parameters were altered as indicated clinically. The baseline score on the 28-item Hamilton Depression Rating Scale (HAMD-28) averaged 34. After 3 months of VNS, 37% of patients had a response (≥ 50% reduction in baseline scores), and 17% achieved remission (HAMD-28 score < 10). At 1 year, response rates increased to 53%, and remission rates to 33%. Sustained response, defined as no relapse during the first year after onset, was observed in 44% of patients, with a median time to response of 9 months. Common side effects included voice alteration (63%) and cough (23%) [15]. These findings led to the FDA approval of VNS for major depressive disorder in 2005.VNS can

now be administered noninvasively through the auricular branch of the vagus nerve, utilizing a method known as transauricular VNS (taVNS). This noninvasive approach streamlines data quantification and enhances accessibility to the technique, thus enabling it to address the need for further research, including double-blind placebo-controlled studies.

THE GUT-BRAIN AXIS AND DEPRESSIVE SYMPTOMS

The gut-brain-axis comprises the multifactorial, bidirectional communication system that involves complex pathways of neural, endocrine and chemokine signaling between the gastrointestinal tract (GIT) and central nervous system (CNS). Components include, but are not restricted to the following:

1. The CNS and ANS, including the vagus nerve.
2. The enteric nervous System (ENS), a complex neural network within the GIT.
3. Hormonal signals, including neurotransmitters (such as 5-HT, D, NE, GABA, Ach) and gut hormones (e.g., ghrelin, leptin, CCK).
4. The immune system, represented by cytokines, chemokines, and gut-associated lymphoid tissue (GALT).
5. Barrier systems such as the blood-brain barrier (BBB) and the blood-gut barrier, which regulate the passage of molecules between the gut and CNS.
6. The human microbiome, comprising diverse microorganisms that contribute to this communication system.

It is to be noted that the human microbiome is sometimes considered a separate system that also has communication pathways with the brain, which overlap with those of the GIT and the gut-brain-axis is by some authors extended to a tripartite communication system.

These components collectively form a comprehensive framework for understanding the reciprocal nature of the connection between the GIT and the CNS.

The vagus nerve plays a significant role in this system, receiving signals from both GIT nervous plexuses, the plexus of Meissner and the plexus of Auerbach, and transmitting them to the nucleus tractus solitarius (NTS) [16]. In the following, we will discuss the main neural pathways by means of which the vagus nerve can inhibit or stimulate nuclei in the brain.

Figure 1 illustrates the main pathways of the vagus nerve and its projections to the brainstem and brain nuclei. The solitary tract nucleus (NTS) serves as the principal relay station for projections that include the hypothalamus via the periventricular nucleus (PVN), the pituitary gland, amygdala, locus coeruleus, substantia nigra (SN), and the hippocampus via the median septum. These structures are involved in major processes such as behavioral modulation and cognitive functions, in conjunction with the limbic system.

The cell bodies of the vagal afferents transmitted to the NTS from the stomach lie in the medial and gelatinous nuclei, while the medial and commissural nuclei host the cell bodies of the fibers that transmit signals from the intestines. The NTS, located in the dorsal aspect of the medulla, projects to the dorsal raphe nucleus and periaqueductal gray matter, as well as behavioral and emotional-regulating networks that include the limbic system.

From the NTS, a series of projections are present that play a role in the regulation of mood, cognition, and behavior [18]. These projections include pathways to the hippocampus via the medial septum, the amygdala, and the locus coeruleus, which further relays signals to the dorsal raphe nucleus. Additionally, the NTS projects to the hypothalamus via its periventricular nucleus (PVN), which connects to the VTA and pituitary gland, and to the parabrachial nucleus (PBN), which itself relays signals to the central nucleus of the amygdala (CeA). Activation of the PBN-SN (substantia nigra) pathway results in reward-related behavior, while activation of the PBN-CeA pathway evokes avoidance behavior [18].

Vagus-mediated pathways

An additional implication supportive of the case is that the above mentioned vagus-mediated pathways are

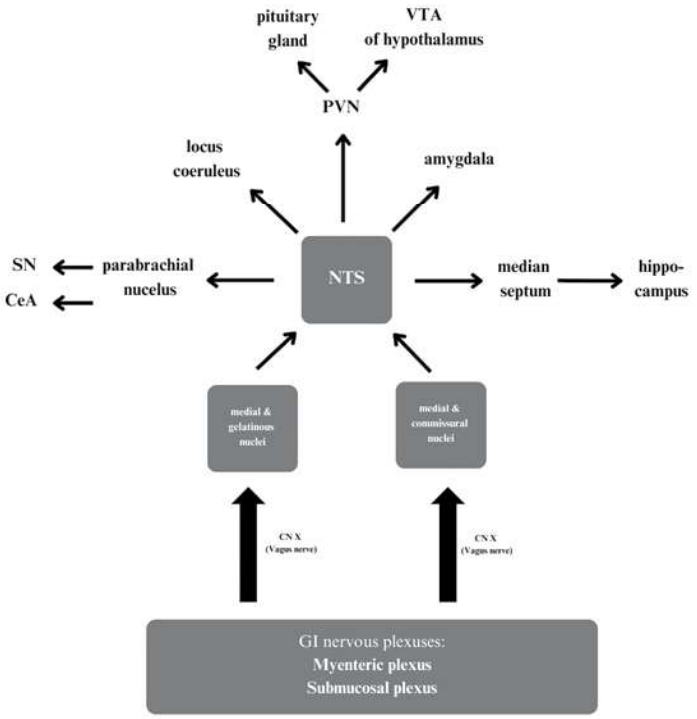

Fig. 1. Vagus nerve pathways and regulatory systems

also influenced by gut bacteria, pathogenic or commensal. One instance involved administering subclinical doses of C. jejuni to CF1 mice, while the control group received saline. This resulted in increased anxiety behaviors and FOs immunoreactivity in the vagal afferent cell bodies, as well as in the NT [19]. Another finding is that Lactobacillus rhamnosus induces relieve of anxiety by GABAAα2 receptor reduction in the amygdala. This effect was then blocked following vagotomy, indicating that the vagus nerve might have been a contributor to the effect by communication projections to the NTS and ultimately, the amygdala [20].

Finally, while many studies have shown that the gut microbiota influences gene expression in the cortex, the exact neuronal pathways mediating these changes have yet to be determined.

CLINICAL AND ANECDOTAL EVIDENCE

The lack of reported cases of "post-vagotomy depression" in humans is a notable observation in the literature. This may be attributed to the fact that depression is a common condition with multifactorial etiologies, including psychological stress, traumatic experiences, neurochemical imbalances, chronic medical conditions, and lifestyle factors, which may coincide with the time of surgery. Alongside with this, depressive symptoms take time to develop (and thus may not be implemented into data collection). It is also not intuitive to consider depression as a postoperative complication in data collection. These factors obscure the potential correlation between the incidence of depression and vagotomy or vagus nerve ablation.

Sporadic reports exist, such as a 1978 publication where 38 patients were subjected to transthoracic vagotomy with overall good results, yet one patient died from a psychiatric condition (vital depression) three months after his second intervention [21]. A clinical study that investigated psychological factors and their impact on surgery outcomes in patients with peptic ulcer disease who underwent either Polya partial gastrectomy or total vagotomy concluded that patients with late response of gastric acid secretion following insulin had significantly higher scores of neuroticism [22]. The outcome thus shows that the degree of vagus nerve dysfunction was associated with a higher rate of neuroticism.

Whether a significant undercount of post-vagotomy depression existed in the pre-anti ulcer drug era is unclear due to lacking data. Nowadays vagotomy is not anymore a common procedure and is an indication for recurrent peptic ulcer disease (PUD), Zollinger-Ellison syndrome as well as Gastroesophageal reflux disease (GERD) that is unresponsive to pharmacological treatment.

Given the potential benefits of VNS, it is plausible that improper activation of vagus-dependent pathways may lead to, or exacerbate, cognitive disorders, mood disorders, and behavioral disturbances. Although this has not yet been proven, ongoing research increasingly supports the possibility of a causal relationship.

PROPOSED HYPOTHESES AND FUTURE RESEARCH DIRECTIONS

Vagotomy in mice has been studied for links to depression. Such is the case with a study conducted on mice who underwent celiac vagotomy which attenuated the anti-depressive effects of fluoxetine and also attenuated the restraint stress or cefaclor-induced reduction in serotonin levels and Htr1a mRNA expression in the hippocampus [23]. This finding suggests that fluoxetine response can be altered by impaired vagus nerve function.

Another study induced depression in mice by common bile duct ligation (CBDL), a procedure used to induce cirrhosis in mice. A series of symptoms appeared, and CBDL also induced depression-like symptoms in mice which in continuation of the study were reversed by undergoing subdiaphragmatic vagotomy [24].

Vagotomy, thus, can both induce and alleviate depression, and whether the former or latter sets in depends on the nature of the preceding intervention. It is of interest for further research to investigate how this knowledge might apply to clinical practice. Vagus nerve stimulation alleviates depression or brings it to remission in a smaller percentage of cases. In reverse, insufficient stimulation of the vagus nerve due to structural or biochemical compromise may exacerbate depression in predisposed individuals or even cause de novo depressive disorders.

Behavioral testing of depression in rodents

Based on the conclusions observed in this review, our hypothesis is that anatomical and physiological malfunction of the vagus nerve in humans may (to an extent that is currently unknown) contribute to the development of affective disorders and similar behavioral disturbances. The smallest scale on which this can be tested is by using vagotomized rodents to observe any significant behavioral changes after the intervention. Identifying an appropriate model of behavioral testing is crucial for this research and will help to assess the reliability of the phenotypic differences in the vagotomized rodents.

In the study of animal models, three criteria are applied to test the reliability of an animal model of depression [25]. Face validity is the degree of resemblance of the depressive state in humans. Construct validity is the similarities in etiology, like chronic exposure to stress or deprivation of monoamines as is the case in the reserpine-induced model [26]. The last criterion is predictive validity, which is the predictability of therapeutic re-

sponse, as has been demonstrated to be the case with the administration of Tetrahydroisoquinoline amines in the reserpine-induced model, which reverses the depression phenotype [27].

All three criteria must be considered in investigating the intervention mentioned (vagotomy) for its potential as a model of depression. The factor which has already been proven to have some reliability in this model is the predictive validity, as demonstrated by Joo et al., where celiac vagotomy significantly attenuated the antidepressive effects of fluoxetine [28]. This suggests that hypothetically the monoamine balance in the CNS can be altered if the vagus nerve is compromised.

CONCLUSION

In conclusion, this review highlights how previously unexplored pathways of mood regulation may play an underestimated role in the development of affective disorders. The strongest argument for the implications of this review is the efficacy of VNS in treating major depressive disorder. If research in this field continues to yield positive therapeutic results, it should prompt the scientific community to further explore the mechanisms underlying the relationship between depression and vagus nerve functions.

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