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DERLEME / REVIEW

Brain-Gut Network in Inflammatory Bowel Diseases and the Role of Vagal Nerve in Neuroinflammation

İnflamatuvar Bağırsak Hastalıklarında Beyin-Bağırsak Ağı ve Nöroinflamasyonda Vagal Sinirin Rolü

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SUMMARY

In both normal and pathological situations, the brain and gut communicate. Intestinal inflammation is crucial in the progression of systemic inflammation and neuroinflammation. Inflammatory Bowel Diseases, neurodegeneration, and neuroinflammation all benefit from elucidating the molecular relationships between the gut and the brain. Crohn's disease, ulcerative colitis, and indeterminate colitis are chronic disorders characterized by recurring episodes of gastrointestinal inflammation. Inflammatory bowel disease has evolved into a global disease in the 21st century, affecting around 6.8 million individuals and increasing in prevalence. According to growing evidence using clinical, epidemiological, and experimental data, Inflammatory Bowel Disease predisposes people to central nervous system disorders. The goal of this review is to address current knowledge in inflammatory bowel disorders, to analyze the interconnections between Inflammatory Bowel Diseases and neurodegenerative and neuroinflammatory diseases all along the gut-brain axis, and to emphasize the role of neuroinflammation in Inflammatory Bowel Diseases. Finally, we address vagal nerve stimulation as a potential treatment because it is a critical component of brain-gut interactions and exerts a dual anti-inflammatory role via its afferent and efferent fibers.

Keywords: Inflammatory bowel diseases, brain-gut axis, microbiota, neuroinflammation, neurodegeneration, vagal nerve stimulation

ÖZ

Hem normal hem de patolojik durumlarda beyin ve bağırsak iletişim kurar. Bağırsak iltihabı, sistemik iltihaplanma ve nöroinflamasyonun ilerlemesinde çok önemlidir. İnflamatuar Bağırsak Hastalıkları, nörodejenerasyon ve nöroinflamasyonun tümü, bağırsak ve beyin arasındaki moleküler ilişkilerin aydınlatılmasından yararlanır. Crohn hastalığı, ülseratif kolit ve nedeni belli tam olmayan kolit, tekrarlayan gastrointestinal inflamasyon atakları ile karakterize edilen kronik bozukluklardır. İnflamatuar bağırsak hastalığı, 21. yüzyılda yaklaşık 6,8 milyon kişiyi etkileyen ve prevalansı giderek artan küresel bir hastalığa dönüştü. Klinik, epidemiyolojik ve deneysel veriler kullanılarak artan kanıtlara göre İnflamatuar Bağırsak Hastalığı, insanlarda merkezi sinir sistemi bozukluklarına yatkınlık yaratıyor. Bu derlemenin amacı inflamatuar barsak bozukluklarındaki güncel bilgileri ele almak, İnflamatuar Bağırsak Hastalıkları ile bağırsak-beyin ekseni boyunca nörodejeneratif ve nöroinflamatuar hastalıklar arasındaki bağlantıları analiz etmek ve İnflamatuar Bağırsak Hastalıklarında nöroinflamasyonun rolünü vurgulamaktır. Son olarak, vagal sinir stimülasyonunu potansiyel bir tedavi olarak ele alıyoruz çünkü bu, beyin-bağırsak etkileşimlerinin kritik bir bileşenidir ve afferent ve efferent lifleri yoluyla ikili bir anti-inflamatuar rol oynar.

Anahtar Sözcükler: İnflamatuar bağırsak hastalıkları, beyin-bağırsak ekseni, mikrobiyota, nöroinflamasyon, nörodejenerasyon, vagal sinir stimülasyonu

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Introduction

The brain and the gastrointestinal tract are the primary sensory organs in charge of functions such as perception, integration, and transmission of data from the internal and external environments (1), and they communicate in two directions. The brain-gut axis is a regular information loop critical in controlling homeostasis. Maintaining this two-way communication appears to result from a complicated system involving endocrine systems, immunological systems, neurological systems, metabolic systems, and the vagus nerve (2,3), (Figure 1). In addition, the gut is a vital control center for the immune system, and the

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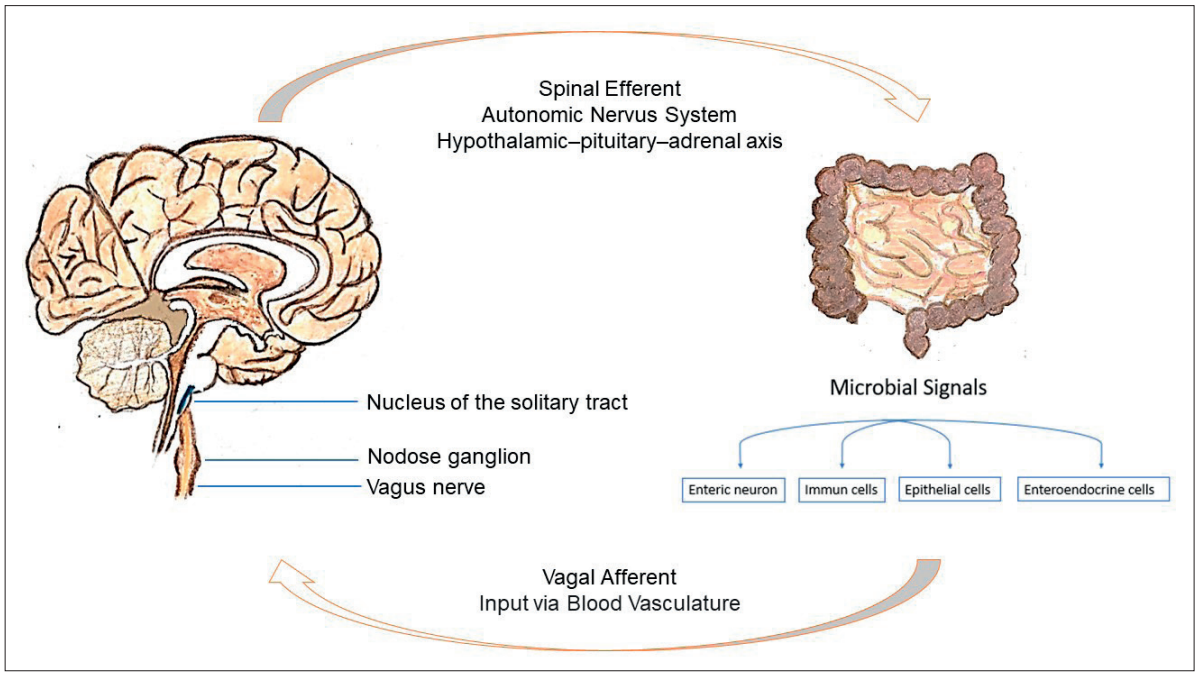

Figure 1. Gut-Brain Axis. The gut-brain axis has a two-way communication system driven by neural, immunological, hormonal, metabolic, and microbial signals.

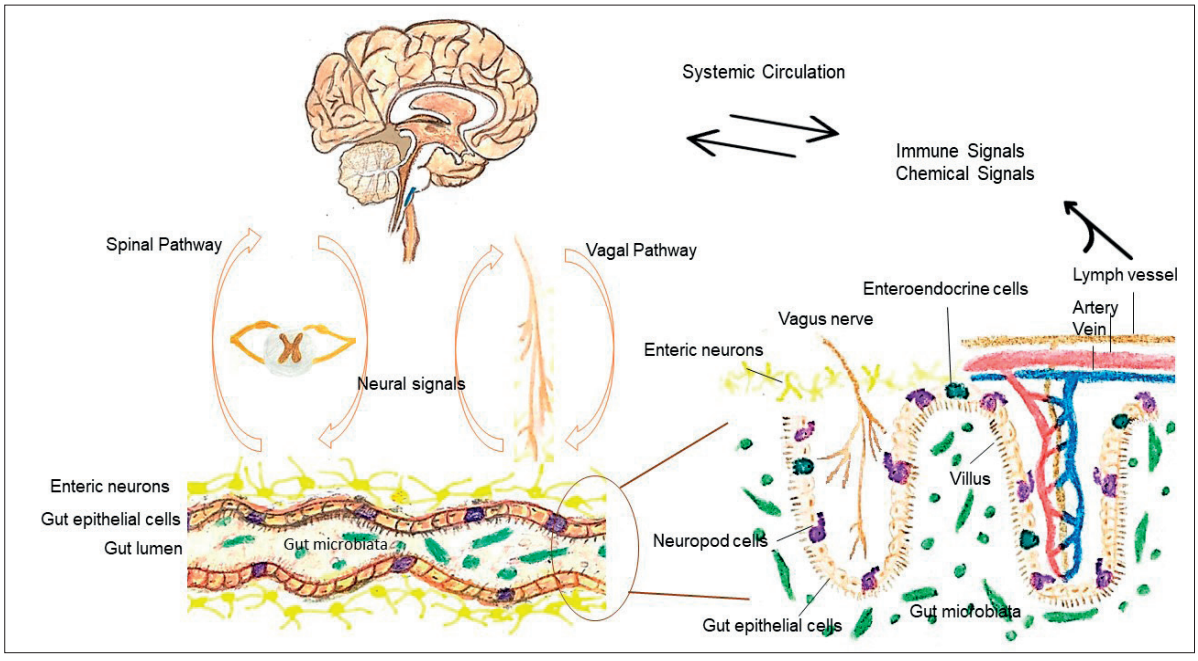

Figure 2. Intestinal innervation components

vagus nerve is essential in immune modulation (3). According to current studies, bidirectional communication along the gut-brain axis is crucial in modulating inflammatory pain perception, responses, and immunological homeostasis (1).

The enteric nervous system (ENS) is a crucial modulator of gut barrier function and an essential component of enteric homeostasis. (2). The ENS produces around 30 neurotransmitters and has a large number of neurons. Hormones and peptides produced into the bloodstream by the ENS (for example, ghrelin) can cross the blood-brain barrier and function with the vagus nerve to regulate different activities (3), (Figure 2). In vagus-related investigations (e.g., vagotomy), there is growing evidence that alterations in the microbiota content send enteric nervous system messages via the vagus (4).

The afferent spinal and vagal sensory nerves convey feedback from the intestines to the spinal cord and the solitary nucleus from the viscera. They achieve this by activating polysynaptic inputs to higher brain regions such as the hypothalamus and

limbic forebrain. This communication involves brain pathways, hormones, and immunological signals (5).

The composition of the human microbiome is unique in each individual. Accumulating evidence suggests that the gut microbiome has a critical role in brain health, regulating the normal functioning of this axis and homeostasis (2,6).

Inhibitory and excitatory neurotransmitters are primary in brain function, including learning and memory, movement, affect, and communication. Intestinal bacteria produce several neurotransmitters and neuromodulators, including GABA, serotonin, norepinephrine, dopamine, histamine, and acetylcholine, which can have direct effects on the brain (2). Glutamate, GABA, Acetylcholine, and serotonin (except the precursor tryptophan) cannot cross the blood-brain barrier. Still, it can act on the enteric nervous system and vagus nerve (7). Short-chain fatty acids (SCFAs), long-chain fatty acids (LCFAs), propionate, and conjugated linoleic acid are neuroactive metabolites produced by the microbiome; these metabolites indirectly affect the brain by modulating immune function, inflammation, and neurogenesis (2). A breach in the gastrointestinal barrier may raise the risk of infection and inflammation (8).

Neurodegenerative diseases and neurodevelopmental disorders frequently exhibit ENS dysfunction (3). The data gathered from experiments conducted without microbes, with antibiotics in the diet, and with microbiota transplantation offers us indications that intestinal diseases and changes in the microbiome (change due to probiotics, bacteria, pathogen or another factor) are not only limited to the intestine, but also affect the basis and variables of many neurological and psychiatric diseases such as metabolic disorders, schizophrenia (9), autism spectrum disorders (10), allergies and asthma (11), depression, and IBD (12).

In particular, it significantly affects tryptophan metabolism, the serotonergic system, stress, mood regulation, and immunity. Serotonin is an important neurotransmitter in both components of the brain-gut network. Compared to serotonin levels in the brain, serotonin levels in the gut are high. The enterochromaffin subtype of enteroendocrine cells and serotonergic neurons of the myenteric plexus are involved in serotonin secretion. Tryptophan (TRP) is an essential amino acid mainly metabolized in the liver. TRP metabolism is involved in pathways linked to the gut-brain axis and associated with the severity of irritable bowel disease. Approximately 90% of TRP is converted to kynurenine for the kynurenine pathway (KP), with the remaining being metabolized to serotonin and indole. The immunological response to IBD significantly impacts KP metabolism (2,6).

Inflammatory Bowel Diseases

Inflammatory bowel disease (IBD) is a chronic idiopathic disorder that leads to inflammation of the gastrointestinal tract, and it has emerged as a global disease in the 21st century. Recent epidemiological studies have indicated that the illness burden of IBD is increasing in developing countries (13).

The frequency of IBD is rapidly increasing in Western countries, causing a significant workload and difficulty for gastroenterology professionals. For instance, the prevalence of IBD in the U.S. was 0.5% in 2015, and it is anticipated that 2.2 million Americans will have the condition by 2025 if the current trend continues. Although people of European heritage are more likely to have IBD, newly industrialized areas such as Asia, the Middle East, and Africa have seen substantial rises in incidence (14).

The financial and resource burden from IBD on healthcare systems is significant. As the global prevalence of these diseases rises, it is critical to forecast future loads to prepare healthcare systems for the challenges of increased numbers of patients, comorbid disorders, prolonged disease course, and aging populations (15).

Etiopathogenesis of Inflammatory Bowel Diseases

Dietary changes from the Western diet, such as the consumption of refined, high-fat foods and nutritional additives, as a result of the co-evolution of humans and their gut microbiota from a high-fiber ancestral diet, may play a role in the increasing incidences of IBD in countries that are industrializing and westernizing (16). Physical activity, obesity, stress, antibiotic use in childhood, low levels of vitamin D, sleep, and smoking are all risk factors for developing IBD. Diet, which might have a pro-inflammatory effect, is one of the critical components in IBD pathogenesis and prognosis (14,17).

Inflammatory bowel disease pathophysiology is complex and only partially understood (18). The causes of these disorders have been linked to interactions between genetic, host, dysbiosis, immunological, and environmental factors. IBD's genetic components have long been known. Twin studies have revealed more excellent concordance for Crohn's disease (CD) and ulcerative colitis (UC), with CD having up to 58% concordance among monozygotic twins. Furthermore, the underlying causes of IBD also include diversity of the host microbiome, changes identified in the host microbiome, an increase in mucolytic bacteria that cause a deterioration in the epithelial barrier, as well as an increase in bacteria that adhere to the intestinal epithelium such as Proteobacteria, the effect of some pharmaceuticals on the microbiota and nutrition (17).

Clinical Features and Diagnosis of Inflammatory Bowel Diseases

Inflammatory Bowel Diseases are classified as chronic inflammatory autoimmune diseases (6).

Ulcerative colitis (UC) originates in the rectum and extends proximally. Abdominal pain, rectal bleeding, and diarrhea are common symptoms. Cramps characterize IBD. This type of IBD is characterized by cramps, a decrease in red blood cells, weight loss, as well as a high fever. One out of every ten pediatric patients develops a severe illness. Serious complications, such as bleeding, an enlarged colon, or perforation, may occur in these patients. Crohn's disease (CD) is a chronic condition that can occur anywhere in the gastrointestinal tract and can potentially regress and reoccur. Symptoms of CD include growth retardation, weight loss, and abdominal pain. An indeterminate colitis diagnosis is also used for patients who cannot be classified as CD or UK. It is more common in children. (19).

Inflammatory bowel disease (IBD) represents a group of idiopathic, chronic, inflammatory bowel disorders. The 2 main disease categories are Crohn's disease (CD) and ulcerative colitis (UC). Both of these diseases have overlapping and distinct clinical and pathological features. IBD is a chronic as well as intermittent (involving periods of exacerbation and remission) disease. Symptoms range from mild to severe during relapse and may disappear or decrease in remission (20).

For the correct diagnosis of IBD; It should be based on a combination of patient history, comprehensive physical examination and laboratory findings (blood and stool samples), esophagogastroduodenoscopy (EGD), ileocolonoscopy samples taken from at least 2 sites covering the inflamed area, and imaging of the small intestine. It is important to exclude enteric infections. For example, diarrhea lasting longer than 6 weeks generally distinguishes IBD-associated colitis from most cases of infectious diarrhea (20-22).

Detailed history is critical for diagnosis. It is important to question the patient in detail about the presence of diarrhea, weight loss, vomiting, fistula, fever, the time and duration of symptoms (relapse or remission), whether they affect daily life activities, mood disorders, and additional diseases and infections, travel, smoking, and family history. Mucus or blood in the stool, pain or bleeding during bowel motility, and abdominal pain or cramping may occur. In CD, moderate to severe cramps occur around the navel, often in the right lower quadrant of the abdomen, while in UK they occur in the left lower quadrant. In addition, if bloody diarrhea is often present, or constipation is present, rectal UK may be considered. Nausea and vomiting are more common in CD than in UK (20-22).

Price first used the term indeterminate colitis (IC) in 1978. Indeterminate colitis arises in cases that cannot be assigned to other types of IBD. This condition is more common in pediatrics than in adults (19,23).

In patients with inflammatory bowel diseases, it is usual to experience both relapses and periods of remission. Since the clinical signs, such as diarrhea, abdominal pain, or rectal bleeding, are not diagnostic in and of themselves, the differential diagnosis can be pretty difficult. To properly diagnose inflammatory bowel diseases, it is essential to consider a broad range of inflammatory and viral conditions that share common characteristics with IBD (24).

Anti-inflammatory and immunomodulatory treatments (5-Aminosalicylates, corticosteroids, thiopurines, methotrexate, etc.), microbiome modulators (antibiotics, probiotics, prebiotics, enteral nutrition, Anti-TNF agent and fecal transplantation can be used. If no response is received, surgery can be planned. In 70-75% of CD and UC patients In 20-25% of patients, reduction surgery can be performed, especially segmental resection, bowel-sparing stricturoplasty, ileorectal or ileocolonic anastomosis, temporary ileostomy/colostomy in severe perianal fistula, temporary ileostomy, total proctocolectomy plus permanent ileostomy (20).

Chronic neurodegenerative illnesses all have inflammation in common. Some neurodegenerative disorders are thought to be associated with intestinal dysbiotic conditions (25). During dysbiosis, the signals of bidirectional communication between the brain and the gut become disorganized. This process is associated with altered blood-brain barrier permeability and neuroinflammation (26). Systemic inflammation linked with pathogenic gut microbiota (due to elevated lipopolysaccharide, pro-inflammatory cytokines, and barrier dysfunction) can induce neuroinflammation that exacerbates dysfunctional brain regions, such as the hippocampus and cerebellum. Cognitive impairment may be exacerbated by a dysfunctional vagal-gut-brain axis (8). Dysbiosis (an imbalance between the microbiota and that of the host) contributes to the development of IBD (27).

Accumulating evidence suggests that IBD and Parkinson's share closely connected pathogenic risk factors. Studies indicate that a patient affected by one of these disorders is also susceptible to the other (28). Likewise, there is a two-way link between Multiple Sclerosis and IBD. The cumulative risk ratio for Inflammatory Bowel Disease/ Multiple Sclerosis comorbidities is 1.54, according to meta-analyses of 10 studies involving over a million patients (0.08 percent of whom had both İnflammatory Bowel Disease and Multiple Sclerosis) (29).

Studies indicate that IBD patients are at risk for developing dementia in the future (30). Existing meta-analyses have demonstrated a substantial correlation between CD or UC and the incidence of Alzheimer's Disease in the adult population (31).

Multifactorial pathophysiology underlies both Autism Spectrum Disorders and IBD. Most investigations have shown gut-brain connections with these illnesses (32). According to meta-analyses, those with Autism Spectrum Disorders are more prone to have inflammatory bowel diseases. Children with Autism Spectrum Disorders had a higher prevalence of CD and UC compared to controls (33). Additional causal relationships were with parental, particularly maternal IBD, and autism in offspring (34).

Inflammatory Bowel Disease patients are more susceptible to depression than the general population. It is hypothesized that central nervous system inflammation is responsible for causing depression symptoms (35).

Although these researches provide light on the connections between IBD, neurodegeneration, and neuroinflammation, there are still numerous ambiguities in this field.

Vagal Nerve Stimulation

The autonomic nervous system affects the function of numerous body organs, glands, and involuntary muscles through its sympathetic and parasympathetic divisions (36). The vagus nerve contains sensory and motor components and is an essential part of the autonomic nervous system (37). This nerve, which provides communication between the stomach, intestines, and brain, is the tenth and longest of the cranial nerves (36). The vagus nerve is a critical first-line natural defense against infection/inflammation (38).

The vagal system can modulate inflammation via the afferent pathways of the hypothalamic-pituitary-adrenal axis as well as the efferent pathways of the cholinergic CAIP complex (39-41).

Vagal nerve stimulation (VNS) is a therapeutic treatment approach approved by the European Medicines Agency and the US Food and Drug Administration (FDA) for the treatment of drug-resistant epilepsy and depression (41,48). Vagal nerve stimulation lowers cytokine production. An afferent mechanism inhibits inflammation of the hypothalamic-pituitary tract, while the anti-inflammatory cholinergic vagal pathway is efficient in the efferent component. Activating vagus nerve efferent fibers has an immunomodulatory effect, modulating cytokine production. The neuro-immune communication CAIP allows the host to regulate the immune response and prevent excessive inflammation (38,39).

The vagal nerve can be stimulated both invasively and noninvasively.

In The Invasive Technique, the electrode is surgically opened in the carotid vascular nerve package, which includes the jugular vein, carotid artery and vagus nerve, located under the collarbone, and electrodes are implanted in the cervical vagus nerve. Since the right-sided vagus innervates the cardiac atrium and negative cardiac problems are predicted for the left cervical vagus, implantation is generally performed in the left cervical vagus. In case of cardiac problems (heart failure, etc.), placement on the right side may be preferred (42-44). However, surgical placement of VNS may cause various complications. Cardiac side effects such as hoarseness, cough, bradycardia or asystole, infection, dyspnea and dysphagia can lead to jugular vein injury (42, 45). Researchers think non-invasive VNS, which is easier and cheaper to perform, could be used to minimize surgery-related complications.

In non-invasive applications, the stimulation can be applied to two different locations: neck skin (transcutaneous) and ear (transauricular) (46).

Transcutaneous Vagal Nerve Stimulation

It is transcutaneous vagal nerve stimulation targeting the cervical vagus through the cervical skin. It can be applied unilaterally or bilaterally (43). However, it is thought that the anatomical pathway may limit the speed of vagal stimulation because it contains too many components, or may reduce its effectiveness because it contains both afferent and efferent fibers (46).

Transauricular Vagal Nerve Stimulation

In another non-invasive technique, transauricular vagal nerve Stimulation (tVNS) targets the branch of the vagus nerve (Arnold's nerve) that provides innervation of the cymba concha area located around the auricle (Figure 3). Recent human studies have revealed that tVNS is as effective and safe as VNS but has fewer side effects. Noninvasive approaches seem promising in gastrointestinal system diseases (44).

Vagal Nerve Stimulation in Inflammatory Bowel Diseases

Studies conducted in the last 30 years have contributed to the elucidation of the relationship between Inflammatory Bowel Diseases, the autonomic nervous system, and, in addition to the ENS, the brain-intestinal axis in addition to ENS. It is known that the autonomic nervous system primarily affects intestinal function and is, therefore, effective in diseases such as irritable bowel syndrome. Considering diarrhea and constipation in IBD patients compared to control groups, Differences in vagal cholinergic measurements have been reported in constipation, and abnormalities in sympathetic adrenergic measurements have been reported in diarrhea (47). Inflammatory Bowel Diseases, CD, and UC revealed that some patients exhibited low vagal tone during remission. It has been shown recently that patients with CD with low vagal tone at rest exhibit higher plasma TNF-α levels than patients with high vagal tone. (48). Vagal hypotonia may result from the systemic inflammation seen in IBD or other chronic inflammatory diseases (39).

The modulation of the vagus nerve influences numerous physiological processes and bodily states connected with transmitting information from the brain to the body (49). In animal models of inflammation, such as Colitis, it has been demonstrated that vagal nerve stimulation (VNS) has anti-inflammatory activity (37).

The vagus nerve presents a valuable possibility for bioelectric neuromodulation therapy. The current treatments for IBD include anti-inflammatory and immunosuppressive medicines, anti-

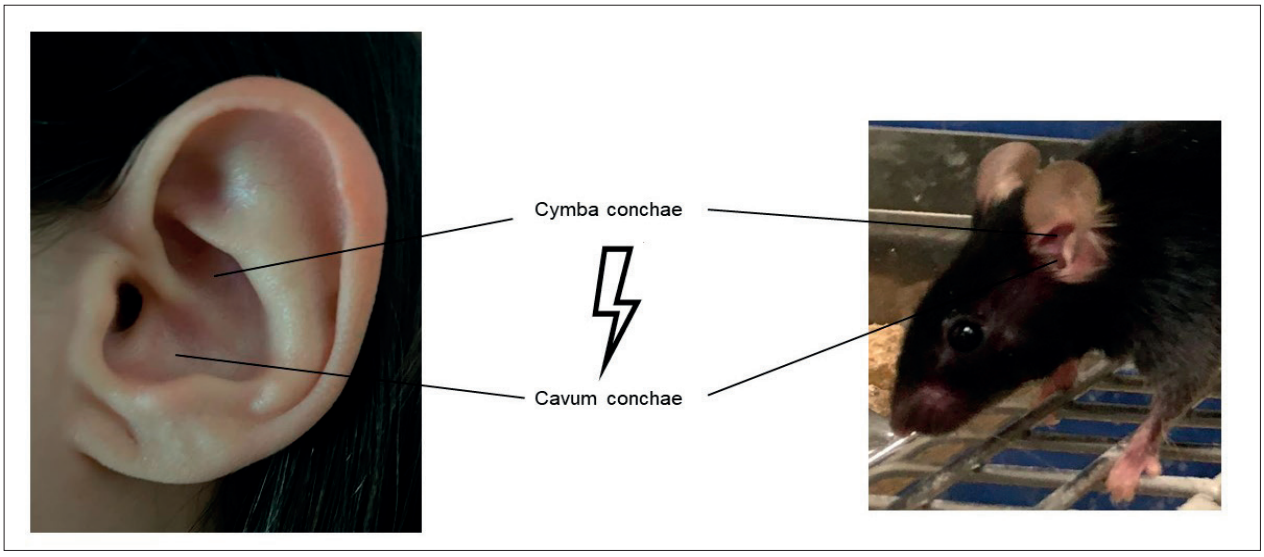

Figure 3. Transauricular vagal stimulation, displayed in human and mice ears

inflammatory medications, and biologic therapy. Antibiotics are administered to reduce the bacterial load in the digestive tract. Among the most significant disadvantages of these treatments are systemic immunosuppression, insufficient impact in some patients, and the development of resistant disease due to long-term drug use. In inflammatory bowel disease, the condition returns after medical treatment has been discontinued. Hence, novel therapies are required (50). Therefore, vagal nerve stimulation under regulated conditions is a possible therapy for Inflammatory Bowel Diseases (39-41).

Conclusion

The incidence of inflammatory bowel diseases is increasing worldwide. Mounting evidence points to the relationships between IBD, neuroinflammation, and neurodegenerative diseases, and brain and gut communication has an essential place in explaining these relationships. The vagus nerve is an essential part of brain-gut communication in both normal and pathological conditions, and stimulation of this nerve is promising for IBD patients.

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