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Navigating the Interplay: Understanding the Potential Impact of the Gut-Lung-Brain Axis on Brain Disorders

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ABSTRACT

The "Gut-Lung-Brain" axis is a complex network involving the gastrointestinal system, respiratory system, and central nervous system, which plays a crucial role in various physiological and pathological processes. Recent research highlights the bidirectional communication along this axis is essential for the development and progression of brain disorders. Understanding the intricate interactions within the gut-lung-brain axis, including the lung-brain, gut-lung, and gut-brain axes, is key to gaining insights into neurological disorders. This understanding can foster interdisciplinary collaboration and facilitate the development of new treatments that consider the multifaceted nature of these conditions.

This comprehensive review delves into the potential contribution of the gut-lung-brain axis to the onset and progression of various brain disorders. It explores shared underlying mechanisms, such as inflammation, that mediate communication between the gut, lung, and brain, shedding light on the complex interplay of these systems. The review also highlights the significant role of the gut-lung-brain axis in shaping neurological, gastrointestinal, and respiratory processes during SARS-CoV-2 pathogenesis, emphasizing the need for a holistic approach to treating brain disorders.

This review enhances our understanding of how proteins, peptides, and metabolites interact within the interorgan communication network. It focuses on the gut-lung-brain axis as a component of this network and explains how these interactions coordinate cellular processes in health and disease. The dynamic interconnection between the gut, lung, and brain emphasizes their mutual reliance and underscores the necessity of addressing brain disorders with a holistic approach.

INTRODUCTION

The “Gut-Lung-Brain” axis is a complex interplay between the Gastrointestinal (GI) system, respiratory system, and the Central Nervous System (CNS), influencing various physiological and pathological processes [1-3]. Emerging research suggests that the bidirectional communication along this axis plays a crucial role in the development and progression of brain disorders [4-6]. Importantly, recent evidence appears to indicate that this communication between the gut and the brain extends beyond traditional realms, involving the respiratory

system as a crucial intermediary [5]. The intricate connections (Figure 1) involve the exchange of signals, immune factors, and microbial metabolites, highlighting the significance of the gut and lung in influencing brain health [7-9].

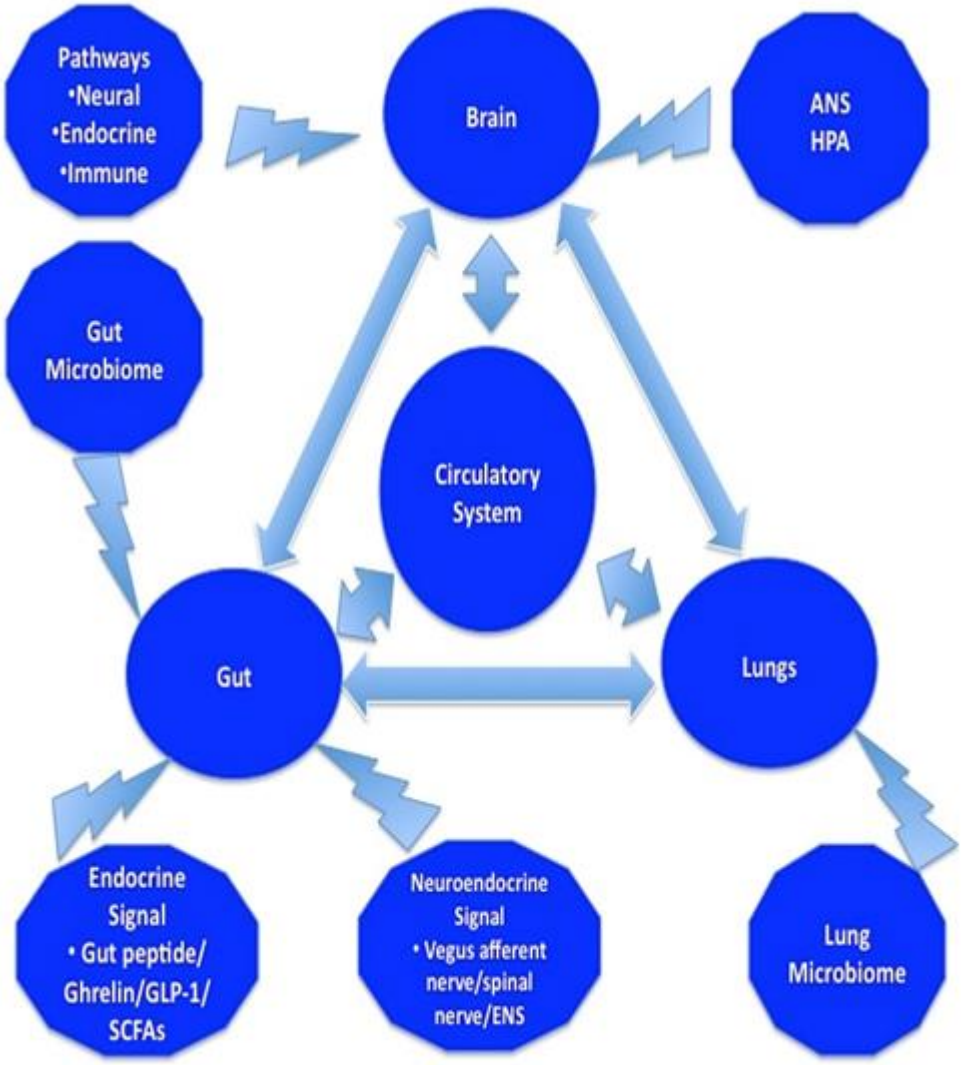

Figure 1: The interconnectedness of the gut, lungs, and brain is crucial for various physiological functions and the development of brain diseases. The central nervous system, particularly the Hypothalamic-Pituitary-Adrenal (HPA) axis, can be activated by environmental factors like emotion or stress. The HPA axis is regulated by complex interactions between the amygdala, hippocampus, and hypothalamus, which form the limbic system. This regulation leads to the release of cortisol into the circulation from the adrenal gland through the activation of Adrenocorticotropic Hormone (ACTH) from the pituitary gland. Simultaneously, the central nervous system communicates with various parts of the intestines, including the Enteric Nervous System (ENS), muscular layers, and gut mucosa, through both afferent and efferent autonomic pathways. This communication influences motility, immunity, permeability, and mucus secretion in the gut. The enteric microbiota plays a role in this communication, as it has bidirectional interactions with these intestinal targets, modulating gastrointestinal functions and being modulated by brain-gut interactions. Metabolites produced by the microbiota, such as Short-Chain Fatty Acids (SCFAs) and gut peptides like GLP-1, impact gut-brain transmission directly and indirectly.

Conversely, the brain can regulate lung function through neuroanatomical, humoral, immunological, and metabolic mechanisms. Dysregulation of the lung microbiome can alter the gut microbiome, leading to dysregulation of Central Nervous System (CNS) functions and ultimately contributing to brain diseases. Despite their distinct anatomical identities, these three organs communicate with each other through substances released into the circulatory system. ANS, autonomic nervous system; GLP-1, glucagon-like peptide-1.

Hence, a thorough understanding obtained from decades of scholarly research on the gut-lung-brain axis-which is made up of distinct parts like the lung-brain, gut-lung, and gut-brain axes-as well as how they interact in the genesis and pathophysiology of brain disorders will aid in the development of new drugs and support public health professionals in developing successful interventional plans that will dramatically reduce the prevalence of brain disorders in the general population [10-12].

Besides, this knowledge will help us better understand the Interorgan Communication Network (ICN), a network of proteins, peptides, and metabolites that interact within the organs to coordinate cellular processes in both health and disease. Importantly, the dynamic interplay of the gut, lung, and brain that constitutes the axis demonstrates the interdependence of organs and emphasizes the need of treating brain disorders holistically [13-15].

Therefore, this comprehensive review explores the potential role of the gut-lung-brain axis in the development and progression of various brain disorders. By delving into neurobiology, it offers a compelling synthesis of existing knowledge, encouraging researchers and clinicians to recognize the interconnected nature of the gut, lung, and brain. This holistic approach invites further investigation into how these organs interact, with the ultimate goal of better understanding and addressing brain disorders.

The rising global burden of brain disorders

Complex and diverse diseases, brain/neurological disorders are mostly caused by malfunctions in the body's autonomic, peripheral, and CNS [16,17]. The impairment of cognitive-motor function is one of the main signs of brain disorders [18]. These impairments are primarily caused by ruptures of the Blood Brain-Barrier (BBB), white matter injury in the brain due to reduced blood flow to the tissue, abnormal amyloid deposition, damage to synaptic plasticity, which leads to dysregulated neural network remodeling, and impaired nerve conduction [19-21]. Consequently, the phrase "brain disorders" encompasses a broad spectrum of diseases, affecting millions of people globally, ranging from neurodevelopmental disorders to Neurodegenerative Diseases (NDs), and is projected to rise over the next few decades as the population ages [22-24].

Additionally, modern lifestyles, characterized by stress, sedentary behavior, and poor dietary habits, contribute to the rise in mental health issues as well. Importantly, individuals with brain disorders often face stigma and discrimination, leading to social isolation and reduce quality of life [25,26]. Furthermore, the financial toll that brain disorders take on societies is substantial because of the expenditures associated with providing care, lost productivity, and healthcare [27].

Neurological disorders are also the primary cause of disability and the second-leading cause of death globally [28]. It is noteworthy that during the past 30 years, the absolute numbers of deaths and impairments attributable to brain disorders have increased dramatically in Low- and Middle-Income Countries (LMICs) [29]. But understanding the prevalence of neurological disorders has become more challenging due to rapid changes in demographics and risk factors including obesity and overweight in both High-Income Countries (HICs) and LMICs [30].

Thus, it is crucial to periodically assess the prevalence of neurological diseases and the underlying factors, including Social Determinants of Health (SDOH), that influence these disorders differently across populations and countries. This comprehensive approach is essential for a thorough understanding of the causes of these diseases [31,32].

Gut-lung, lung-brain, and gut-brain axes: Their physiology and complex interplay

Despite the fact that the gut and lungs are anatomically distinct, the idea that there is a Gut-Lung Axis (GLA) has been reinforced by potential anatomic connections and complex bidirectional networks, particularly involving their respective microbiota [2,33]. As an illustration, the gut and lungs are typically involved in delivering essential two-way communication pertaining to their separate microbiomes, namely the gut microbiota and the lung microbiota. The existence of GLA is clarified by the fact that changes to the gut microbiome can affect the susceptibility of the lung to infection and that alterations to the gut microbial communities can be caused by impairments in respiratory health [33]. Importantly, a unique mucosal immune system that is a part of the GLA is shared by the GI and pulmonary systems [34]. Furthermore, a growing amount of evidence points to a metabolic and immunological axis that links the lungs and the gut [35,36].

Additionally, new data appears to indicate that the "Lung-Brain" Axis (LBA), which regulates physiological processes of the lung and CNS, is also significantly impacted by bidirectional communication between the brain and the lung [4,5]. One of the most important components of the LBA is the vagus nerve, which connects the brainstem to the lungs and beyond [37]. Further evidence also appears to indicate that the lung microbiome regulates the immunological reactivity of the CNS, which influences the vulnerability of the CNS to dysregulated health [38,39]. Another important mediator of the LBA functions is the role of inflammatory molecules, such as cytokines, that are produced in response to lung infections or injury. These molecules have the ability to penetrate the BBB and trigger neuroinflammation, thereby impacting brain health, including cognitive impairment [40,41].

Furthermore, insights into the gut-brain cross talk have uncovered a complex communication mechanism that supports the appropriate maintenance of GI homeostasis and is likely to have numerous implications on motivation, emotional responses, and executive cognitive functions [42,43]. An acronym for the intricacy of these connections is the "Gut-Brain Axis" (GBA). The vagus nerve, which links the brain to the GI tract, is one of the many important channels in the complex bidirectional communication between the gut and brain [44]. This is demonstrated by the fact that up to 50% of patients with cerebral ischemia will develop GI problems, such as dysphagia, GI bleeding, and constipation, all of which are linked to a poor prognosis for stroke patients [45,46]. As a result, the GBA is an essential physiological component of the ICN that influences many biological activities, including the immune system, digestion, mental health, and cognitive processes [47].

Unveiling the triad: Exploring the intertwined dynamics of the gut-lung-brain axis in brain disorders

Despite the fact that the activity of both neuronal and non-neuronal populations significantly influences the physiology and pathophysiology of the brain, mounting evidence over the past few decades has shown that the gut microbiota can regulate the brain's (dys) functions, making it a potential therapeutic target for a wide range of brain disorders [48-50]. For instance, any changes in gut flora, such as dysbiosis, have the potential to cause a wide range of human diseases, including those that affect the brain. On the other hand, lung dysfunctions can elicit or aggravate many brain disorders as well [51,52]. For instance, gas exchange requires a high blood flow

across the lung [53]. The human brain requires the most oxygen of all the other organs combined [54]. Lung diseases can therefore easily lead to brain disorders.

Moreover, recent research seems to suggest that the gut microbiota is important in the pathophysiology and development of long-term lung diseases such as asthma and Chronic Obstructive Pulmonary Disease (COPD), the latter of which often has several extrapulmonary consequences, including brain hypoxia [55]. This underscores the link among the gut, lung, and CNS, and the complex interactions within the gut-lung-brain axis, involving components like GLA, LBA, and GBA. These elements engage in coordinated dialogues to maintain crucial physiological functions, disruption of which can contribute to severe brain disorders.

A crucial piece of information on the possible role of the gut-lung-brain axis in the etiology of Pulmonary Hypertension (PH), a condition frequently accompanied by shortness of breath, dizziness, and chest symptoms, came from a mouse study [56,57]. The mice were subjected to chronic hypoxia (10% oxygen) for four weeks, and the outcomes were compared to those of mice exposed to normoxia in a ventilated chamber. The cumulative results suggest that increased sympathetic and microglial activity, the latter of which is typically linked to neuroinflammation, are involved in the pathophysiology of hypoxia's effects on the heart and lungs [58]. Alongside other signs of gut pathology including a 50% rise in the thickness of the muscularis layer and fibrotic area, there was also a significant decrease in the length of villi and the number of goblet cells in the small intestine. These critical findings from an animal study demonstrated that PH resulted from a dysregulation of the gut-lung-brain axis that affected each of the three organ systems.

Overall, the growing body of research indicates that lung failure can affect the brain through a number of interrelated processes. First, hypoxia can be brought on by low blood oxygen levels, which are often linked to respiratory problems. Prolonged low oxygen levels have been linked to NDs, cognitive decline, and brain cell damage [59]. Second, systemic inflammation can be induced by lung disorders, and inflammatory molecules have the ability to go to the brain and cause neuroinflammation [60]. Numerous neurological conditions are associated with chronic inflammation in the brain. Third, the BBB may alter as a result of lung malfunction, making it easier for deleterious molecules to enter the brain [61]. In addition to other detrimental impacts on brain function, this may result in neuroinflammation. Fourth, the cardiovascular system is frequently impacted by lung disease [62,63]. Cerebral hypoperfusion, which can be brought on by cardiovascular problems including decreased blood flow to the brain, may be a factor in neurological disorders and cognitive loss, and last but not least, the release of cytokines in response to lung injury or infection can affect the brain as well as other organs systemically [64,65]. Also, elevated cytokine levels have been connected to neuroinflammation and NDs [66].

In addition, viral infections, such as respiratory infections, can cause considerable changes in the gut microbiota [67,68]. It is hypothesized that the long-term neurological symptoms of COVID-19 may be related to problems of the intestinal microbiota in these patients, as altered gut microbiota can cause a variety of neurological diseases through neuroinflammation [69,70].

There are several underlying mechanisms that link neuroinflammation and intestinal dysbiosis. First, an increase in intestinal permeability caused by gut dysbiosis is commonly referred to as "leaky gut" [71,72]. This permits the movement of microbiological elements into the bloodstream, including Lipopolysaccharides (LPS). Once in the bloodstream, these substances have the ability to cause inflammation and immunological responses, even in the brain.

Second, several metabolites that are produced by the gut microbiota have the ability to affect inflammation [73,74]. For instance, Short-Chain Fatty Acids (SCFAs) have anti-inflammatory properties, while some microbial products may have pro-inflammatory effects and exacerbate neuroinflammation in the presence of dysbiosis [75].

In light of this, it's critical to emphasize the variety of ways SCFAs can prevent brain disorders through therapeutic effects. Through their inhibition of LPS translocation to the brain, SCFAs reduce neuroinflammation [76]. Additionally, SCFAs regulate the activity of neurotransmitters and apoptosis of neurocytes as well as the inflammatory responses that are mediated by microglia [76,77]. Also, SCFAs may enter the bloodstream and cross the BBB to affect brain functions. Amyloid aggregation in the brain has also been demonstrated to be decreased by SCFAs [78].

Third, pro-inflammatory cytokines can be released from the gut as a result of immunological responses triggered by gut dysbiosis [79]. These cytokines can enter the bloodstream and make their way to the brain, where they can induce neuroinflammation [80].

Conversely, prolonged neuroinflammation can cause NDs via a number of different pathways. Activated immune cells release pro-inflammatory cytokines and other molecules that can damage neurons and disrupt normal cellular function [60,66,81]. Also, neuroinflammation can lead to the production of Reactive Oxygen Species (ROS), causing oxidative stress [82]. This oxidative damage can impair cellular structures and contribute to neurodegeneration. Moreover, inflammatory processes may enhance the release of excitatory neurotransmitters, leading to excitotoxicity, a phenomenon where excessive activation of neurotransmitter receptors damages neurons [83,84]. In addition, prolonged activation of microglial cells, the resident immune cells in the brain, can result in a neurotoxic phenotype, contributing to neuronal death [85,86]. Furthermore, chronic inflammation can hinder the brain's ability to repair and regenerate, further exacerbating damage and contributing to the progression of NDs, and lastly, inflammatory responses may influence the misfolding and aggregation of specific proteins, such as beta-amyloid and tau in Alzheimer's Disease (AD), contributing to the formation of pathological protein aggregates [87,88].

Together, the intricate interplay between inflammatory processes and neuronal function can create a detrimental environment, promoting neurodegenerative changes over time. In this regard, it's crucial to remember that neuroinflammation is a dynamic, complex process, and that the specific function it plays in various NDs may differ. Interestingly, gut dysbiosis can cause chronic fatigue, psychological conditions including sadness and anxiety, psychiatric disorders like Guillain-Barre syndrome, and even NDs like Alzheimer's and Parkinson's Disease (PD), possibly mediated by inflammatory cytokines, GI hormones (e.g., cholecystokinin (CCK)), neurotransmitters such as 5-hydroxytryptamine (5-HT), SCFAs, and the Autonomic Nervous System (ANS) [89-91].

Moreover, in the well-researched case of PD, the pathogenesis is thought to start in the gut. During the early stages of PD progression, accumulating evidence suggests that alpha-synucleinopathy originates in the Enteric Nervous System (ENS) [92,93]. Interestingly, approximately 80% of people with PD have constipation problems, which frequently occur years before the disease is formally diagnosed [94].

On the other hand, Helicobacter pylori has been linked to the release of amyloids and inflammatory mediators, as well as the hyperphosphorylation of tau protein [95]. More causal research must be conducted to better

understand the potential role of the gut microbiota in neurodegenerative or neurodevelopmental disorders, as well as how CNS diseases themselves might change the composition of the gut microbiota.

The pathogenesis of SARS-CoV-2 through the lens of the gut-lung-brain axis

People exposed to SARS-CoV-2 commonly develop a range of symptoms, from mild to severe, such as fever, cough, fatigue, and loss of smell and taste [96]. Additionally, many individuals may also suffer from multiorgan failure, acute respiratory distress syndrome, and pneumonia [97]. Importantly, SARS-CoV-2 can also invade the CNS, which may disrupt the BBB and the synapses of the neuron [98,99]. This may lead to other symptoms, most of which are related to the respiratory system. Additionally, a viral infection like SARS-CoV-2 can cause inflammation and neurodegeneration that can impede efferent transmission to cranial nerves [100]. This can lead to the loss of anti-inflammatory signaling and regular respiratory and GI functions, highlighting the role of the gut-lung-brain axis in mediating brain diseases. Furthermore, SARS-CoV-2 has the ability to infect enterocytes in the gut, leading to gut injury, microbial dysbiosis, and the leakage of bacteria and their byproducts through the compromised epithelial barrier [101]. This process exacerbates both local and systemic pro-inflammatory responses, which can significantly worsen the severity of respiratory disease and greatly impact clinical outcomes. This scenario underscores the intricate interactions among the gut, lung, and brain, which collectively influence respiratory, neurological, and gastrointestinal functions.

Among the numerous mechanisms that can regulate the development of a disease across different organs through various axes, which are beyond the scope of this article, the role of exosomes in mediating disease is one mechanism that warrants discussion. For instance, the metabolites of CNS may communicate between CNS and lung through carrier, the exosome, which is a kind of Extracellular Vesicle (EV) with lipid bilayer membrane, rich in protein, lipid, and nucleic acid, to be able mediate critical cell–cell signal transmission [102,103]. Interestingly, EVs such as exosomes increase in circulation after TBI (Traumatic Brain Injury) [104]. These proinflammatory cytokine-carrying vesicles can be taken up by pulmonary endothelial cells, which then facilitate the production of IL (Interleukin)-1ß and IL-18 by activating the inflammasome and resulting in pulmonary endothelial cells to undergo apoptosis in the end [105,106].

On the other hand, exosomes in the lungs may be able to pass through the BBB and reach the CNS. Evidence seems to suggest that exosome participates in the metastasis of lung cancer into CNS [107]. Exosomes released by lung cancer cells are taken up by brain vascular endothelial cells. These endothelial cells subsequently transmit inhibitory signals to microglia, resulting in a reduction of M1 phenotypic microglia and an increase in M2 phenotypic microglia. It is likely that the shift of microglia phenotypes contributes to the brain metastasis of lung cancer cells [108-110].

Furthermore, according to RNA-Seq analysis of the GSE121307 dataset (which examines the genetic exchange of lung-derived exosomes), recent findings suggest that after SARS-CoV-2 infection, lung-derived exosomes interact with brain microvascular endothelial cells [111-114]. These cells anatomically connect the pathological hotspot of NDs such as Alzheimer's Disease (AD) and Parkinson's Disease (PD) through transcription factors that bind to critical regulatory regions of many genes associated with the development of AD and PD [115,116]. Overall, the intricate interplay within the gut-lung-brain axis underscores the complexity of brain disorders [117-119].

CONCLUSIONS & FUTURE DIRECTION

Taken together, the gut-lung-brain axis is a complex and interconnected system that plays a crucial role in maintaining overall health and well-being. The gut-brain axis, lung-brain axis, and gut-lung axis collectively influence various physiological and pathological processes and play a crucial role in the development and progression of brain diseases.

To put in into an analogy, the gut-lung-brain axis is like a complex symphony, where the gut, lung, and brain play different instruments, each contributing to the overall harmony of health. This symphony is orchestrated by a network of communication pathways involving molecules such as peptides, proteins, and metabolites. Just as a symphony requires perfect coordination among its musicians, the gut-lung-brain axis relies on synchronized interactions to maintain physiological balance and prevent the discord that can lead to brain disorders.

However, further research is needed to fully understand the mechanisms underlying the gut-lung-brain axis and its collective impact on brain diseases and how to intervene gut-lung-brain axis therapeutically to mitigate these diseases.

In concert, several treatment strategies have the potential to prevent and treat neurological disorders and respiratory infections. One such approach is microbiome replacement, which involves restoring a healthy balance of gut microbiota. Additionally, probiotics, prebiotics, and synbiotics can be used to modulate the composition and function of gut microbiota, thereby improving the immune system and restoring balance. These interventions offer promising avenues for enhancing overall health and combating a range of diseases. Additionally, dietary changes, such as increasing fiber intake and reducing fat and sugar consumption, can promote a healthy gut microbiota and improve lung function. Engaging in regular exercise has demonstrated positive effects on both gut microbiota and lung health.

Despite these benefits, further research is essential to investigate the efficacy and potential side effects of such interventions. Recognizing the symbiotic relationship between the gut, lung, and brain is pivotal for comprehensively understanding neurological disorders. This acknowledgment not only encourages interdisciplinary collaboration but also lays the foundation for innovative treatments that can effectively address the multifaceted aspects of these conditions.

Lastly, an in-depth exploration of the ICN, which consists of peptides, proteins, and metabolites interacting within organs to coordinate cellular processes during both homeostasis and stress, holds great promise for understanding disease biology, particularly in the context of the gut-lung-brain axis. Various molecules such as nutrients, waste products, toxins, nucleic acids, proteins, and peptides can act as signaling molecules in this network. Understanding the factors or nodes that connect organs in the ICN could help identify converging or unifying factors responsible for the development of multiorgan diseases, potentially leading to targeted therapeutic interventions.

In summary, a great deal of progress has been made in understanding the intricacies of the ICN over the years, and the lung-brain-gut axis is only one piece of the jigsaw puzzle. Our comprehension of the various ways in which organs communicate with one another and how these disruptions might lead to disease is expected to improve with more research in this field.

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