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The gut-brain axis in schizophrenia: A narrative review from neuroimmunology

El eje microbiota–intestino–cerebro en la esquizofrenia: una revisión narrativa desde la neuroinmunología

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SUMMARY

Schizophrenia is a severe and multifactorial mental disorder that represents a major public health challenge. In recent years, biomedical research has highlighted the role of the microbiota–gut–brain axis as a bidirectional communication system that modulates neurobiological, immunological, and metabolic processes implicated in the pathophysiology of mental disorders. This narrative review critically analyzes the evidence on the relationship between the gut microbiota and schizophrenia, with emphasis on neuroimmunological mechanisms, reported microbial alterations, and potential clinical implications. Observational studies, systematic reviews, and experimental research suggest the presence of intestinal dysbiosis, inflammatory activation, and changes in microbial metabolites in patients with schizophrenia. Finally, the review discusses current methodological limitations and the need for future research to clarify the directionality and clinical relevance of this association.

Keywords: *Gut microbiota, schizophrenia, gut–brain axis, neuroinflammation, mental health.*

RESUMEN

La esquizofrenia es un trastorno mental grave y multifactorial que supone un desafío relevante para la salud pública. En los últimos años, la investigación biomédica ha destacado el papel del eje microbiota–intestino–cerebro como un sistema de comunicación bidireccional capaz de modular procesos neurobiológicos, inmunológicos y metabólicos implicados en la fisiopatología

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de los trastornos mentales. La presente revisión narrativa tiene como objetivo analizar críticamente la evidencia disponible sobre la relación entre la microbiota intestinal y la esquizofrenia, con énfasis en los mecanismos neuroinmunológicos implicados, las alteraciones microbianas descritas y sus posibles implicaciones clínicas. Se revisan estudios observacionales, revisiones sistemáticas y trabajos experimentales que sugieren la existencia de disbiosis intestinal, de activación inflamatoria y de alteraciones en los metabolitos microbianos en pacientes con esquizofrenia. Finalmente, se reflexiona sobre los límites metodológicos actuales y la necesidad de investigaciones futuras que permitan esclarecer la direccionalidad y la relevancia clínica de esta asociación.

Palabras clave: *Microbiota intestinal, esquizofrenia, eje intestino-cerebro, neuroinflamación, salud mental.*

INTRODUCTION

Schizophrenia is a chronic neuropsychiatric disorder characterized by disturbances in thinking, perception, cognition, and behavior, with a significant impact on the quality of life of those who suffer from it and their families (14,15). Worldwide, it is estimated to affect millions of people and is associated with increased morbidity and mortality, as well as significant social and healthcare costs (19,20). Despite decades of research, its etiology remains incompletely understood and is currently recognized as resulting from a complex interplay among genetic, neurobiological, environmental, and psychosocial factors (13,14).

In this context, scientific interest in the role of the gut in brain health has resurfaced strongly. Historically, the digestive system's relevance to overall health was recognized; however, in recent decades, the gut microbiota has been identified as an active component in regulating multiple physiological functions, including those related to the central nervous system (1). The gut-brain axis has been proposed as an integrative model that explains the bidirectional communication between the gastrointestinal tract and the brain through neuronal, endocrine, and immunological pathways (1,2).

Several studies have indicated associations between alterations in the composition of the gut microbiota and neuropsychiatric disorders, including depression, anxiety, and schizophrenia (2-5). These observations have generated increasing interest in exploring the microbiota as a potential modulator of neuroinflammatory and neurochemical processes involved in the pathophysiology of schizophrenia. This narrative review critically analyzes the available evidence on this relationship, highlighting the main findings, their implications, and the current limitations of our knowledge.

Gut microbiota: fundamental concepts and development throughout life

The gut microbiota is defined as the collection of microorganisms that stably inhabit the human gastrointestinal tract, including bacteria, archaea, viruses, and fungi. Collectively, these microorganisms and their genetic material constitute the gut microbiome, which far exceeds the size of the human genome (1,16). The microbiota plays essential roles in metabolism, protection against pathogens, immune system development, and regulation of intestinal homeostasis.

The establishment of the gut microbiota begins at birth and is influenced by factors such as mode of delivery, breastfeeding, diet, antibiotic use, and environmental factors (1,7). During the first years of life, the microbiota undergoes dynamic changes until it reaches a relatively stable composition in adulthood. However, this stability is relative, as the microbiota can be modified throughout life in response to dietary and pharmacological factors, as well as aging (1,11).

From a clinical perspective, these variations are relevant due to their potential impact on immunological and neurobiological regulation. Alterations in microbial composition, known as dysbiosis, have been associated with various inflammatory, metabolic, and neurological pathologies (8,9). In the field of mental health, it has been suggested that gut dysbiosis could contribute to the alteration of neurochemical and neuroinflammatory mechanisms, opening an emerging field of research in biological psychiatry.

The gut-microbiota-brain axis: communication mechanisms

The gut-brain axis is a complex bidirectional communication system involving the gut microbiota, the enteric nervous system, the immune system, and the central nervous system (1,2). This interaction occurs through multiple pathways that act in an integrated manner.

1. Neural pathways

One of the main communication pathways is the neuronal pathway, mediated by the enteric nervous system and the vagus nerve. The microbiota can influence neuronal activity by producing neurotransmitters and neuromodulators, such as gamma-aminobutyric acid, serotonin, and acetylcholine, which can activate vagal afferents to the brain (1,8,9). This pathway allows signals originating in the gut to modulate brain functions related to mood, cognition, and stress response.

2. Immunological pathways

The immune system is another key component of the gut-brain axis. It is estimated that a significant proportion of the body's immune cells are located in the gastrointestinal tract, where they interact closely with the microbiota (1). Immune activation induced by gut microorganisms can lead to the release of proinflammatory cytokines that influence brain function, either via the systemic circulation or by disrupting the blood-brain barrier (10,12).

3. Endocrine and metabolic pathways

The gut microbiota also participates in endocrine regulation through modulation of the hypothalamic-pituitary-adrenal axis and the production of microbial metabolites, such as short-chain fatty acids. These compounds can exert neuroactive and anti-inflammatory effects, contributing to brain homeostasis (2,4). Alterations in these metabolic mechanisms have been linked to neuroinflammation and cognitive dysfunction.

4. Neuroinflammation and immune dysfunction in schizophrenia

Accumulating evidence suggests that schizophrenia is associated with a state of low-grade inflammatory activation, both peripherally and centrally (18,24). Studies have described elevated concentrations of proinflammatory cytokines and alterations in microglial function, supporting the neuroimmunological hypothesis of the disorder (10,12).

In this context, the gut microbiota emerges as a potential modulator of the inflammatory response. Dysbiosis could promote the translocation of bacterial components and the activation of the immune system, contributing to neuroinflammatory processes implicated in schizophrenia (3,4). However, the available evidence is predominantly observational and does not permit the establishment of clear causal relationships, underscoring the need for cautious interpretation.

5. Alterations in the intestinal microbiota in patients with schizophrenia

Recent literature describes consistent differences in gut microbiota composition between individuals with schizophrenia and healthy controls. Several observational studies and systematic reviews have reported a reduction in short-chain fatty acid-producing bacteria, particularly butyrate, along with an increase in pro-inflammatory taxa (3-5,12,29-31). These changes have been interpreted as indicators of gut dysbiosis that may be relevant to the disorder's pathophysiology.

Among the most frequent findings are decreases in bacterial families associated with anti-inflammatory functions and intestinal barrier maintenance, and increases in bacteria linked to metabolic endotoxemia (5,30,31). However, the results show considerable heterogeneity between studies, attributable to methodological differences, sample sizes, diagnostic criteria, diets, and concomitant use of psychotropic drugs (3,29,34).

It is important to emphasize that most available studies are cross-sectional in design, which limits causal inference. Consequently, it is not possible to determine whether microbial alterations preceding the onset of schizophrenia are a consequence of the disorder or reflect the impact of associated factors such as lifestyle and pharmacological treatments (12,31).

6. Modulating factors: diet, drugs and psychoactive substances

The composition of the gut microbiota is highly sensitive to external factors, including diet, medication use, and psychoactive substance use. In the context of schizophrenia, these elements become particularly relevant due to their potential modulating effect on gut dysbiosis (2,4).

Dietary interventions have been shown to influence microbial diversity and function. High-fiber, plant-based diets have been associated with more favorable microbial profiles and reduced inflammatory markers. At the same time, dietary patterns characterized by high consumption of ultra-processed foods have been linked to dysbiosis (2,21). The use of probiotics and prebiotics as complementary strategies in patients with schizophrenia has also been explored, with preliminary results suggesting modest improvements in some clinical and biochemical parameters. However, the evidence remains limited (4,30).

On the other hand, chronic use of psychotropic drugs, especially antipsychotics, can alter the gut microbiota, complicating the interpretation of findings observed in clinical studies (31). Finally, the use of psychoactive substances, such as cannabis, has been associated with specific changes in microbial composition in patients with schizophrenia. However, the available data are scarce and require confirmation in methodologically rigorous studies (6,39).

7. Current clinical and therapeutic implications

The growing interest in the microbiota has generated expectations regarding its potential clinical application in the management of schizophrenia. From a translational perspective, it has been suggested that modulating the microbiota could improve psychiatric symptoms or reduce the inflammatory burden associated with the disorder (2,5).

However, current evidence does not support recommending microbiota-based interventions as standard treatments. Available studies are heterogeneous, with small sample sizes and variable results (30,31). Therefore, based on current knowledge, the microbiota should be considered a potential modulator rather than a primary therapeutic target in schizophrenia.

Even so, the study of the microbiota offers opportunities to advance a comprehensive understanding of the disorder and to identify patient subgroups that could benefit from personalized interventions in the future, always underpinned by an evidence-based approach and clinical prudence.

Methodological limitations and knowledge gaps

Despite the growing number of publications, research on the microbiota and schizophrenia remains limited. Observational studies and narrative reviews predominate, with a scarcity of well-designed clinical trials (3,26,40). Furthermore, the lack of standardization in microbiological analysis methods hinders comparisons between studies and the replicability of results.

Another relevant challenge is the directionality of the association. It has not been clearly established whether gut dysbiosis plays a causal role in schizophrenia or whether it constitutes an epiphenomenon associated with other factors of the disorder (7,26). Furthermore, most studies do not adequately control for confounding variables, including diet, medication use, and lifestyle.

Adopting quality standards and FAIR principles in research, as well as developing longitudinal studies and controlled trials, is essential to advancing this field (26,40).

Final reflection

The reviewed evidence suggests that the gut microbiota is part of a complex neuroimmunological network that may influence the pathophysiology of schizophrenia. However, reducing the disorder to a microbial alteration would be an inappropriate simplification of a multifactorial and heterogeneous condition.

From a reflective perspective, the study of the gut-brain axis invites us to rethink reductionist models and to promote integrative approaches that account for the interactions among biological, environmental, and social factors. The microbiota thus emerges as another component within a complex network, the understanding of which requires rigorous, collaborative research.

CONCLUSIONS

Schizophrenia is a complex and multifactorial disorder involving neurobiological, immunological, and environmental processes. Within this framework, gut microbiota has emerged as a significant component of the gut-brain axis, capable of modulating mechanisms that influence brain function and immune responses.

The reviewed studies concur in describing alterations in the composition of the gut microbiota in people with schizophrenia, characterized primarily by dysbiosis and a pro-inflammatory profile. These microbial modifications have been linked to neuroinflammatory processes and to changes in metabolites of neurobiological interest, supporting the hypothesis of bidirectional interactions between the gut and the central nervous system in this disorder.

However, these findings should be interpreted with caution. Most available research uses observational designs and has methodological limitations that prevent the establishment of clear causal relationships between the gut microbiota and schizophrenia. Consequently, it is not possible to determine whether microbial alterations preceding the development of the disorder are a consequence of it, or reflect the impact of associated factors such as diet, psychotropic medication use, or lifestyle.

From a clinical perspective, strategies aimed at modulating the gut microbiota, including dietary interventions, probiotics, and prebiotics, show encouraging preliminary results; however, these are insufficient to recommend their systematic application in the treatment of schizophrenia. These results suggest that the gut microbiota could be a potential modulator rather than a primary therapeutic target.

Finally, this review underscores the need to strengthen future research through longitudinal studies, well-designed clinical trials, and rigorous methodological standards, including the FAIR principles. An integrative and judicious approach to the gut-brain axis will advance a more comprehensive understanding of schizophrenia, contributing to evidence-based, responsible, and scientifically sound psychiatry.

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