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Gut Microbiome and Brain: Scope and Perspectives

Microbioma intestinal y cerebro: alcances y perspectivas

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An amazing example of symbiosis is that observed between intestinal bacteria and their hosts, with its implications for the regulation of the functions and development of the metabolic, immune, and nervous systems through a bidirectional interaction along the gut-brain axis. These complex communications feature connections through signals from the immune, neural, and chemical systems, which have a crucial impact on health and the understanding of mental and neurological diseases. Previously, diseases related to the nervous system and neurological involvement had been considered to originate from brain alterations arising from changes in perfusion or structural abnormalities that evolved into atrophies or abnormalities of the white and gray matter; however, these explanations were limited as per the function and development of the nervous system, and did not take into account changes in the metabolic and immune status of the organism (Cryan et al., 2020). Current research is beginning to uncover how microorganisms present in the gut influence the brain through their ability to produce and modify immunological, metabolic, and neurochemical factors, directly impacting the nervous system (Morais & Mazmanian, 2021). This perspective has led to large numbers of research that correlates the composition of microbial communities, and their function, with neurodevelopmental defects, e.g., Autism Spectrum Disorder (ASD), in addition to other mental illnesses such as anxiety, schizophrenia, and mood disorders (Bastiaanssen et al., 2019). Moreover, the microbiota-gut-brain axis has been repeatedly associated with neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (Morais & Mazmanian, 2021; Bastiaanssen et al., 2019).

By analyzing these preclinical research models of the microbiota-brain axis, it has been possible to determine that some features of the central nervous system are conserved across species (Morais, 2021), making it possible to study certain behavioral characteristics, including inferring it in the expression of human emotions. These investigations have contributed to understanding the mechanisms of the microbiota-gut-brain axis. Nevertheless, it is extensively accepted that preclinical models designed to study human behavior are limited. Thus, although they are used as tools to study certain phenotypes that are similar across species, they are not designed to complete study the human phenotype in only one model.

In this regard, a promising approach to bridge this gap is the use of animals transplanted with human feces mentioned as "humanized animals". These models are being increasingly used in studies to assess and analyze the contribution of the gut microbiota in human brain diseases. However, it must be recognized that gut microbiomes are considerably dissimilar between species, and it is still necessary to develop techniques that maintain and stabilize microbial engraftment when transferring microbiomes between different species (Cryan et al., 2020). In addition, behavioral disorders such as neurodegenerative disorders generally have heterogeneous expression and underlie multifactorial conditions, with symptoms fluctuating between people and over time. At the experimental level, several approaches exist around the close correlation between gut microbiota conformation, brain homeostasis, and the pathophysiology of various neuropsychiatric and neurological illnesses. However, examples of mechanistic descriptions supporting these connections are still limited; this is partially due to the fact that interactions between the intestinal microbiota and the brain often involve several ways of interaction (immunological, endocrine, neural, etc.), and could require microbial factors produced by varied bacteria (e.g., the production of short-chain fatty acids (sCFA), shared in numerous bacterial lineages). Although this field of research on the intestinal microbiota and the brain is new, even in relation to other areas of neuroscience, modern tools and innovative techniques have been developed and will permit an increasing progress in the molecular characterization of the pathways concerned in the microbiota-brain axis.

From this perspective, findings on the microbiome-gut-brain axis in ASD and Parkinson's disease stand out. ASDs are neurodevelopmental disorders whose estimated global prevalence since 2012 has shown changes within and between regions, with a prevalence of 100/10,000 (range: 1.09/10,000 to 436.0/10,000) (Zeidan et al., 2022). The symptomatology of people with ASD initiates in childhood and extends into adulthood. They present significant difficulties in their communication and behaviors in family, school, and social contexts, presenting a variable range of interaction behaviors (Lord et al., 2018), from exhibiting restrictive and stereotyped behaviors to aggressiveness, self-injury negativism, and irritability, which causes a problem with compliance of social norms and carries a significant burden of dysfunctionality for the sufferer (Hervás & Rueda, 2018).

Recently, attempts have been made to model the pathophysiological mechanisms involved in ASD. In this regard, the high prevalence of gastrointestinal symptoms, ranging from 70 to 90% of patients, suggests the presence of intestinal dysfunction (Adams et al., 2011; Gorrindo et al., 2012). Likewise, some studies have indicated that these gastrointestinal problems tend to be more recurrent in ASD than previously described in neurotypical patients (Vuong & Hsiao, 2017).

Besides the bowel dysfunction previously associated with the ASD population, reported correlations with core symptoms of autism —such as sleep disturbances, communication and language impairments, and high levels of anxiety and irritability (Attlee et al., 2015)— suggest a close involvement between the gut microbiome and the nervous system for ASD (Margolis et al., 2021); thus, it can contribute to explain alterations of neural systems in brain structures, such as the amygdala, basal ganglia and prefrontal cortex (Alamoudi et al., 2022; Casanova et al, 2013), involved in social behavior, behavioral control, and emotional regulation. This would be explained by variations in the enteric nervous system, which is controlled by the gut microbiome and the immune system (Margolis et al., 2021).

So far, studies suggest that in ASD the gut microbiota is involved in the levels of neurotransmitters such as γ-aminobutyric acid (GABA) (Strandwitz et al., 2018), glutamate, oxytocin, and serotonin (Sharon et al., 2019), involved in the etiopathogenesis of the disorder. Additionally, microbial effect on the immune system plays a key function in determining neuroimmune responses in ASD, assuming that chronic low-grade inflammation is present in subjects presenting with this clinical condition (Sharon et al., 2019). Furthermore, the degree to which microbial metabolites (e.g., taurine, 5-aminovaleric acid, bile acid metabolites, and cccFA) impact ASD symptoms is becoming more obvious, and new knowledge are applied to this new area of investigation to better understand the mechanisms involved in ASD, i.e., how diet, genetic factors, and environment influence the intestinal microbiome and how preclinical models are used to estimate microbial composition, offering a target for further preclinical modeling studies, and their relationship to behavior in ASD.

On the other hand, regarding neurodegenerative diseases, PD is of special interest. This disease presents with motor impairment (parkinsonism), with an asymmetric onset that is maintained as the disease progresses. In addition to the "typical" motor symptoms, sleep disorders and executive dysfunction are observed and progress with the evolution of the disease, as well as behavioral problems such as apathy, depression, and fatigue, observing variable sensoperceptive changes (Saavedra Moreno et al., 2019).

PD is at the moment the second most frequent neurodegenerative disease after AD; in 2016, approximately 6 million people in the world had the disease, and by 2020 approximately one million subjects in the United States were diagnosed with PD. Overall, it has been indicated that by 2040 there could be around 17 million people worldwide, i.e., it could become the fastest grow-

ing neurological disease globally (Saavedra Moreno et al., 2019; Weintraub & Mamikonyan, 2019).

While there are multiple ways in which the intestinal microbiota contributes to PD and includes microbial products that affect protein stability and induce inflammation (among other consequences), it also intervenes through its metabolic processes in the aggregation of phosphorylated α-synuclein (αsyn) (Blandini et al., 2000), both in the gut and in the brain. Indeed, it has been shown how intestinal microorganisms can modulate inflammation in several preclinical models of PD, which is principally pertinent to explaining how αsyn-mediated pathology and progression in the neurodegenerative process are triggered. Thus, it could be considered how the intestinal microbiota modulates the therapeutic efficacy of levodopa (l-dopa), so far one of the main molecules for PD treatment, since certain gut bacterial species produce enzymes able to degrade this medicine before it gets to the brain (Rekdal et al., 2019; van Kessel et al., 2019).

As a preliminary conclusion, we could say that the growing evidence from both preclinical and clinical settings offers a convincing proof that the communication between the intestinal microbiota and the mammalian nervous system outlines both adaptive and dysfunctional neurological courses. The three main ways in which the microbiota can influence nervous system function and development are: modulation of the immune response; direct effects on metabolism, including neuropeptides, hormones, and neurotransmitters; and direct results on neurons and their signaling. Thus, the co-evolution of animals and their associated microbial groups appear to have given rise to multifaceted biological interactions between the gut and the brain, an attractive prospect that needs further research, but likewise offers promising new roads for behavioral modulation, especially that pertinent to the study of neurodegenerative and psychiatric disorders.

Many vital inquiries about the gut-brain axis are still unanswered. While it appears that microbial metabolites are significant for communication along this axis, it is still unclear what number of effects may occur over hormonal and/or neural routes, let alone how many metabolites directly disturb the brain after crossing the blood-brain barrier. Microbial metabolites may also act directly on peripheral nervous system routes, such as the enteric nervous system, altering the interaction between the periphery and the central nervous system. The barriers to understanding the mechanisms of action in this new field are closely related to the intricacies of human neurological disorders and the limits of preclinical systems that struggle with the study of human diseases.

The fields of neuroscience and microbiology, besides other disciplines, need close collaboration to develop complete and relevant perspectives to establish the action mechanisms of findings that presently remain observational, along with response labors in translating these innovations to improve human health. A modern and integrative interpretation of traditional brain disorders as whole-body conditions, embracing an important role for the gastrointestinal tract, may bring new strategies to modulate the intestinal microbiota to deliver new, effective, and safe therapeutic possibilities for the better treatment of neuropsychiatric and neurodegenerative diseases.

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