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CHAPTER 22

Gut-Brain Axis: The role of gut microbiota in immune and neurological homeostasis

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ABSTRACT

The knowledge of the interaction between the gut microbiota and the central nervous system is growing more and more with surprising discoveries, especially in how it influences aspects of human health. It is worth noting its influence on the regulation of the immune system, based on the production of metabolites. Another important factor in this relationship is the behavior of the blood-brain barrier and the production of neurotransmitters, such as serotonin, which directly impact humoral characteristics and brain function. Not far away, the microbiota is related to the appearance of neurodegenerative and immunological diseases in specific cases. Thus, it is very important to highlight strategies that promote a healthy microbiota with the aim of preventing and treating these conditions, such as therapeutic perspectives with an emphasis on the role of prebiotics and probiotics that act directly in the maintenance of intestinal and brain health.

Keywords: Gut-brain, Microbiota, Neurotransmitters, Blood-brain barrier, Enteric nervous system, Neurodegenerative diseases.

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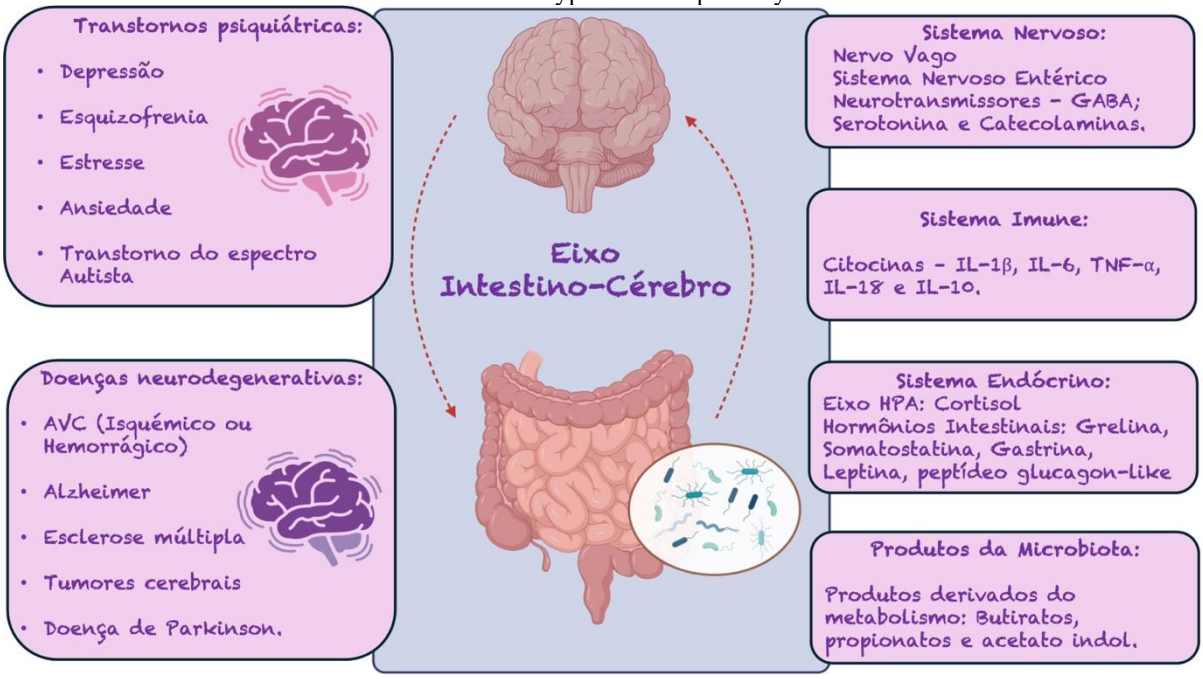
INTRODUCTION

The field of neurogastroenterology studies the interaction between the brain and the gut, highlighting the great importance of the connection between these two systems, which may initially seem quite distinct. The gut-brain axis is a complex network of communication that involves the enteric nervous system, the central nervous system, and the gastrointestinal tract. This interaction is not only limited to the transmission of motor and sensory signals related to digestion, but also plays a role in emotional, behavioral, and cognitive regulation.

In this interaction, a very important component must be taken into account, the gut microbiota, a diverse community of trillions of microorganisms, bacteria, viruses and fungi. Unlike the pathologies that are usually associated with these organisms, this interaction, in this case, exerts a dominance over human physiology by modulating food digestion and the regulation of the immune system (**Figure 1**)

Figure 1. Schematization of the Gut-Brain axis, highlighting the systems involved and their products. In addition, the clinical correlations involved in axis imbalance. PAH: Hypothalamic-pituitary-adrenal.



In this chapter, we will learn about how the gut microbiota modulates an interaction with neurotransmitters, such as serotonin and gamma-aminobutyric acid (GABA), and immune functions. In this way, we will explore how signals from the intestine act through the enteric nervous system, influencing not only food digestion, but also humoral regulation, stress response, and even the development of immunological diseases, such as Parkinson's disease and multiple sclerosis (**Figure 1**).

These scientific discoveries are redefining our understanding of the relationship between the gut and the brain, revealing a complex interplay in which mind and body intertwine in surprising ways, with direct impacts on health and well-being.

GUT MICROBIOTA AND IMMUNITY

The intrinsic interaction between these systems, as described above, presents a large field of research in the most varied themes and discussions, such as the diet based on the predominant Western diet, that is, a diet based on the intake of red meat. This diet, if not properly regulated, can lead to a picture of microbiota dysbiosis, since it alters the balance of macrobiotic metabolites, such as short-chain fatty acids (SCFAs) and trimethylamine pro-atherogenic N-oxide (TMAO), which is a result of choline and carnitine that are in the composition of red meat. This imbalance interferes with a higher risk of developing cardiovascular diseases, mainly due to TMAO. It is also possible to infer that the low amount of foods with fiber causes a reduction in the production of SCFAs, as in the case of butyrate, which will have consequences in the increase of intestinal permeability along with an increase in bacterial toxins in the bloodstream. This cascade of events stimulates the innate immune system, which will be another factor in the increase in cardiovascular disease and a prescriber for the development of insulin resistance.

In this way, dysbiosis, by stimulating the innate immune system, implies its dysregulation by increasing immune activity in the body's own cells. Not only the factor described above, the development of autoimmune diseases such as type 1 diabetes mellitus, is also related to antibiotic treatments, cesarean deliveries and poor breastfeeding are contributing factors to this condition. To understand how this microbial dysfunction is responsible for the autoimmune picture, it is necessary to understand that the imbalance between the innate and adaptive systems through bystander activation mechanisms and molecular mimicry.

Molecular mimicry has its functioning briefly described from the moment when an immune response against a specific microbiotic agent causes a cross-reaction against the organism's own epitopes. Consequently, the persistence of this adaptive immune reaction against this microorganism tends to lead to an increase in the epitopes against which an autoimmune response arises, even though the initial foreign body has already been eliminated. One of the ways to circumvent this problem related to the dysregulation of the immune system is based on a promising therapeutic approach, fecal microbiota transplantation (FMT), which has the potential to prevent or delay autoimmune and autoinflammatory diseases.

Not only mimicry, it is essential to understand bystander activation to understand the whole general picture of the situation, since it represents a phenomenon in which the immune system is prolonged activated due to the constant presence of certain microorganisms that results in an increase

in autoreactive T cells that also start to "fight" the body's own antigens. These microorganisms, in addition to being related to the condition of providing antigens to the immune system, start to produce short-chain acids (SCFAs) that further intensify the autoimmune response process.

So far, it has been possible to understand how dysbiosis is related to an increase in the development of cardiovascular diseases and the emergence of autoimmune situations, however this whole picture leaves "traces" and "traces" for complications in patients with sepsis, acute respiratory distress syndrome. All this disturbance to the host has a strong negative effect on the diversity of the intestinal microbiota, this reduction is responsible for making the body more susceptible to opportunistic infections, greater risks of kidney dysfunction and decreased muscle mass. This whole picture tends to lead to a cycle of recurrent infections with greater losses of the intestinal microbiota and a reduction in the correct functioning of the immune system, thus reaching sepsis. In this sense, as a consequence of the fragility mentioned above, the excessive growth of the microbiota caused by sepsis and the translocation of microorganisms from the intestine to the respiratory tract, there is an induction of systemic inflammatory responses in which all these events indicate that sepsis is an unbalanced immune reaction to an infectious agent, in which the immune response against the agent is compromised and there is excessive inflammation, due to the increased passage of bacteria from the gut into the bloodstream.

In addition to all the information presented so far, it is very important to remember and describe that the intestinal microbiota plays a fundamental role in the maturation of the immune system after birth, regulation of the entire system and in the self-antigen response throughout the individual's life. Thus, the imbalance of the microbiota is one of the factors responsible for the emergence of conditions that lead to the appearance of immune dysregulations, such as allergies, autoimmune and inflammatory diseases.

From tests carried out in mice that did not present germs, that is, without the presence of the microbiota, it was possible to identify malformation of the lymphoid organs, especially in the spleen and mesenteric lymph nodes, as a consequence of which they had reduced intestinal Peyer's plates with less presence of TCD4 cells and IgA deficiency.

The microbiota is also responsible for modulating the immune system by producing molecules with immunomodulatory and anti-inflammatory properties that are capable of influencing immune cells. Among them are the short-chain fatty acids (SCFAs) mentioned above, which, through signaling through receptors such as GPR109A/HCA2, play an essential role in the regulation of immune homeostasis and in the balance of immune tolerance and responses to pathogens. This interaction actively participates in the production of regulatory T cells (Tregs). Not only SCFAs, there is the production of metabolites derived from indole and polyamines that exert immunomodulatory functions, such as the integrity of the intestinal mucosa, from indole, which contributes to the

strengthening of the defense barrier against pathogens and stimulates the production of antimicrobial substances and intestinal goblet cells.

It is also possible to measure that the microbiota can influence the presence of bone mass in the body. It is known that the main cause of bone loss is the result of estrogen deficiency after menopause, this occurs due to an imbalance of bone renewal and resorption caused by the effect of estrogen on the immune system. This deficiency of the hormone causes an increase in the production of pro-inflammatory and pro-osteoclastogenic cytokines such as TNF, alpha and RANKL, which directly affect this balance. Thus, studies in rats free of the intestinal microbiota showed changes in bone mass, but the results are conflicting and inconclusive, since it was possible to identify an increase in this mass while other studies showed negative effects due to the reduction of the IGF-1 level. Antibiotic studies have also shown divergent results on bone density varying exposure time, age, sex, and treatment protocols.

In mice free of the microbiota, it was possible to identify a reduced number of osteoclasts and lower levels of pro-inflammatory cytokines in the bones and alterations in the immune system, as previously seen. Such characteristics normalized from the moment these animals began to be raised with the presence of the microbiota. These studies reveal something new and surprising about the interaction of these two systems, but they require more research to fully understand this interaction.

It is worth mentioning that the interaction between the immune system and the microbiota occurs through a two-way pathway, that is, both influence each other. In this case, it is possible to observe such interaction in the control of microbial composition and compartmentalization on the balance between mucosal and lumen bacteria, carried out by the immune system, where an outer layer of mucus in the colon acts as a reservoir of microorganisms that contributes to restoring the microbiotic balance in any disturbances. It is also worth mentioning the importance of peptides and antimicrobial receptors in the small intestine, which play a similar role in defending against the entry of pathogenic bacteria.

Another interaction of great importance for the human body is the development of antigen-presenting cells (APCs), such as dendritic cells and macrophages. Because it is possible to identify that a dysbiosis can lead to a reduction in mature APC cells. Some studies have indicated that bacterial colonization can induce the recruitment of gastrointestinal dendritic cells and influence the differentiation of Th17 cells.

Therefore, based on all the information contained in this chapter, it is undeniable that there is an intense and gigantic relationship between the intestinal microbiota and the immune system, a bidirectional interaction that interferes with the entire homeostasis of the human body, from the immune response to a simple pathogen to the development of serious autoimmune diseases and bone

health in general. Thus, understanding this interaction is necessary for the development of therapeutic and preventive strategies for a wide variety of health conditions.

BLOOD-BRAIN BARRIER AND NEUROTRANSMITTERS

The blood-brain barrier (BBB) plays a very important role in the integrity of the nervous system by participating in the control of the flow of substances between the bloodstream and brain tissue. In the previous topic it was possible to observe how the intestinal microbiota actively participates in the modulation of the immune system as well as in other parts of the body, now it will also be possible to identify how microbiotics act on the integrity of the barrier and what are their effects on it.

Initially, it is important to consider that short-chain fatty acids (SCFAs) are fundamental to understand this interaction, which will be described and understood throughout this topic. Its production is correlated by the fermentation of dietary fibers in the colon. They are basically composed of three compounds with influence on the subject to be treated, acetate, propionate and butyrate, each with specific proportions in the lumen of the colon. These acids are absorbed by the intestinal mucosa and can be detected in the blood in varying concentrations.

It was possible to observe in a study that butyrate has beneficial effects on the barrier, such as the positive regulation of tight junction proteins. It was also identified that animal tests, that oral administration of sodium butyrate or colonization with bacteria that produce this substance, resulted in a decrease in the permeability of the blood-brain barrier and a better preservation of it after traumatic brain injuries. In addition, the intraperitoneal administration of butyrate showed improvements in cases of neuroinflammation in elderly mice, whereas in transgenic mice with loss of synaptic and neuronal learning, intracerebroventricular applications had effects on the improvement of learning and memory in these animals, that is, an eventual therapeutic potential in the recovery of brain injuries.

Other SCFAs, such as propionate, have also shown neuroprotective, anti-inflammatory, and permeability-reducing effects in studies with human brain endothelial cell culture models. However, high brain levels of propionate may be related to exacerbated symptoms in certain neuropsychiatric conditions, such as autism. A condition that can be mitigated with butyrate supplementation, which shows that the balance between these substances is crucial, not only the individual levels of these metabolites. In addition, SCFAs participate in the maturation of microglial cells, which maintain the integrity of the BBB.

A small observation can be made with regard to recent studies that found nucleic acids and proteins derived from bacteria, viruses and fungi were detected in the brains of deceased individuals with Alzheimer's disease. Such discoveries raised the possibility that these microbial metabolites,

such as SCFAs, may be produced locally, that is, by infiltrating microbes present in the brain, something very important for the development of a "brain microbiome", however this idea still presents controversies around its existence. In this same study, it was possible to identify the presence of immunostains that provide information on the presence of fungal species in brain tissue in these same patients, such as *Candida albicans*, which is typically identified in mammalian intestines. Its observation occurs in the forms of buds and with hyphae, which suggests a growth within the brain tissue. However, it remains uncertain whether gut microbes have significant impacts on the availability of SCFAs within the brain through "local residents."

Trimethylamine (TMA) is another metabolite produced by the gut microbiota of great importance for understanding this interrelationship. To understand its practical effect on the body, it is necessary to be aware of its production, which occurs through compounds such as choline, lecithin, carnitine and trimethylamine oxide-N (TMAO) that are present in certain foods. Regarding TMAO, it is important to note that its presence in large quantities at plasma levels is associated with an increased risk of neurodegenerative diseases, such as Alzheimer's, increased chances of colorectal cancer and cardiovascular diseases. In addition, not only its negative effect, it is also worth mentioning that this compound has shown therapeutic potential in conditions such as Alzheimer's, again, by restoring the ability of the TAU protein to promote the assembly of microtubules essential for neuronal function. This shows that the concentration of this substance is fundamental for what the effect will be on the body.

In addition to the metabolites already mentioned, such as SCFAs and TMAO, it is important to remember amino acids such as tryptophan, which also participates in the regulation of brain health. This compound is metabolized by the microbiota in order to produce neurotransmitters, such as gamma-aminobutyric acid (GABA), which plays a crucial role in the central nervous system, by acting mainly as an inhibitor, that is, decreasing neuronal activity, helping to regulate neural excitation and maintain balance in the brain. In addition to these functions, it is worth mentioning that it participates in the reduction of anxiety, induces sleep, controls muscle tone and plays a role in pain modulation. Thus, it is possible to infer that the microbiota plays a very important role in the modulation of the nervous system and homeostasis in general.

In the same way that amino acids play essential roles in maintaining brain health, vitamins produced by the gut microbiota are also essential for this occurrence, such as vitamin K, which is associated with the prevention of Alzheimer's disease, and the modulation of fibrillation of alpha-synuclein, a protein linked to Parkinson's.

Regarding the modulation of the nervous system by means of neurotransmitters, it is possible to highlight that its influence on the serotonergic system occurs in addition to the presence of a deficiency of the intestinal microbiota, since the administration of probiotics "*Bifidobacterium*

infantis" in mice results in reduced concentrations of 5-hydroxyindoleacetic acid (5-HIAA), which is a metabolite of serotonin, in the frontal cortex along with significant values of plasma concentrations of tryptophan and kynurenic acids. Such studies are essential because they confirm the ability of the gut microbiota to exert a great influence on the serotonergic system.

In addition, the microbiota not only directly uses tryptophan, but is also able to metabolize it, which reduces its availability to the host. It is noteworthy that certain bacterial strains harbor the enzyme tryptophanase, which mediates the reaction of producing indole 3-acetic acid (IAA) from tryptophan. Such enzymatic capacity is associated with gastrointestinal abnormalities in autism spectrum disorders. However, this process of IAA production from tryptophan is not completely understood, but it is of great importance to further understand this relationship, since it is already known that certain specific bacterial strains can produce serotonin from tryptophan *in vitro*.

In the previous topic it was possible to identify how the intestinal microbiota interferes in the functioning of the immune system through various mechanisms and actions, while in the current one it was possible to understand that the microbiota also interferes in serotonergic modulation. Thus, as serotonin modulates immune responses, as evidenced by the association of 5-HT receptors in immune cells, in view of the above, this is another way that the intestinal microbiota interferes with the immune system.

In addition to modulating the release of neurotransmitters and influencing the blood-brain barrier, the microbiota is also present in the behavioral and humoral influence of human beings. Some studies have shown that there is a clear change in the microbiota in mice with depression. Not only in animal trials, administering a combination of probiotics to healthy volunteers has also been shown to alleviate psychological distress, including depressive symptoms. In addition, there is clinical evidence that proves the efficacy of antibacterial agents, such as minocycline, in modulating depression.

Previously, some effects of serotonin and how the microbiota interferes with its presence in the human body have been described, according to this, some metabolites of tryptophan, which include this neurotransmitter, play a crucial role in the pathogenesis of anxiety and depression. Certain medications that increase serotonin availability, such as selective serotonin reuptake inhibitors (SSRIs), MAO inhibitors (MAOIs), and tricyclic antidepressants (TCAs) play an important role in reducing depressive symptoms. Thus, the advancement in the understanding of the composition of the intestinal microbiota has verified the contribution they have to the development and clinical phenotype of these diseases.

Another study demonstrates the above by revealing greater anxiety behaviors in mice without microbiota compared to conventionally reared mice. However, the behavioral normalization of these

animals does not occur easily with microbial repopulation, which indicates the existence of a critical period for the occurrence of its influence.

GUT DYSBIOSIS AND NEUROLOGICAL AND IMMUNOLOGICAL DISEASES

The gut microbiota is notably essential for several processes of the nervous system, such as neurogenesis, myelination and microglial activation and is capable of modulating behavior and cognition, in addition to being responsible for altering the susceptibility and progression of neurodegenerative diseases. In this way, it is believed that the pathogenesis of diseases such as Parkinson's Disease (PD) and multiple sclerosis is closely linked with the imbalance of the gut - gut dysbiosis.

In terms of prevalence, PD is one of the fastest growing neurological diseases worldwide and although it is primarily defined by motor symptoms such as tremors and muscle stiffness, it is interesting to note more than 200 years ago, in the first formal description of the disease, James Parkinson recognized that gastrointestinal dysfunctions were part of the clinical spectrum of the disease. He further speculated that PD could have its roots within the gastrointestinal system.

It should be noted at the outset that the gut microbiome, composed of billions of microorganisms, evolves along with the host to form a complex mutualistic relationship, so that the gastrointestinal tract provides a nurturing environment for the microbial community, while the microbiome performs a wide range of essential functions that influence host physiology.

This host-microbiome interaction, along with individual microbiome variability in response to lifestyle changes, is important when interpreting disease-related changes in gut microbiome composition and function. Because aging is an integral contributor to the pathophysiology of PD and exerts a significant influence on the gut microbial ecosystem, it is crucial to consider these factors.

Studies have revealed that people with PD tend to have an increased abundance of certain beneficial bacteria, such as *Akkermansia* spp., *Bifidobacterium* spp., and *Lactobacillus* spp. These bacteria play important roles in gut health and are often found in probiotic preparations. The increased abundance of *Akkermansia* spp. has been associated with slow colonic transit and low body weight and/or fat mass, common characteristics in individuals with PD.

Importantly, the role of a single microbial species cannot be considered in isolation, but rather within a community context that takes into account the net effects of bacteria sharing similar metabolic functions versus those with contrary actions. This more comprehensive understanding is essential to understanding how the gut microbiome may be involved in the pathophysiology and progression of not only PD but also other neurological diseases.

Thus, it is evident that some intestinal problems and interventions, in addition to dietary factors, may be associated with a subsequent risk of developing and progressing PD. For example,

constipation, inflammatory bowel disease, irritable bowel syndrome may implicate in the pathophysiology of the disease.

Another pathology constantly related to gut dysbiosis is multiple sclerosis (MS), a disease that contrasts with Alzheimer's disease (AD) and Parkinson's disease (PD), mainly affecting young adults, especially females. It is a demyelinating disease of the central nervous system (CNS) with an inflammatory component: it is characterized by chronic inflammation in both the white and gray matter of the brain and spinal cord, which causes the destruction of the myelin that covers neurons. Although the mechanisms underlying MS are not yet fully understood, it is postulated that an unsatisfactory functioning of the immune system is the most likely cause of the disease. In addition to chronic inflammation, an alteration in the selectivity of the blood-brain barrier in the brain of MS patients has been observed. This state facilitates the migration of immune cells (mainly T cells) to the nervous system and penetration into the brain. After infiltration into the CNS, T cells begin to recognize myelin as a trigger for the immune system, which causes increased inflammation and results in demyelination.

The pathophysiology of MS may also be linked to genetic and environmental factors. Early obesity, reduced levels of vitamin D in the blood, and insufficient exposure to sunlight, as well as smoking, are the causes most frequently described in the literature. All of these aspects can also indirectly affect the gut microbiota – as microbes can control immunity by regulating T cells, the gut microbiota has received attention as an important factor in MS pathology.

In recent studies, it has been shown that there are considerable differences between stool samples from MS patients and samples from the control group (with healthy subjects). Samples from MS patients revealed decreased levels of Bacteroidetes spp. *Clostridium* spp., *Faecalibacterium* spp. and *Prevotella* spp. (the latter produces propionate, which is an SCFA). In addition, an increase in the abundance of *Methanobrevibacter* spp. and *Akkermansia muciniphila* was observed in different types of the pathology. In addition, it is interestingly demonstrated that transplanting the microbiota of MS patients into germ-free mice resulted in intensification of experimental autoimmune encephalomyelitis (EAE), a type of demyelinating disease in animals, in contrast to germ-free mice treated with healthy microbiota. These results suggest the potential involvement of the microbiota in the development of MS and its impact on disease progression.

Recent evidence suggests that immune system activation in MS originates in the gut. Other studies report that altering the immune response in MS triggers changes in the gut microbiota. Establishing the triggering event is difficult: is it inflammation of the gut or the brain?

In addition, attention to the intestinal microbiota has also been shown to be important in the field of rheumatology, with the possibility of positively impacting patients in the area. However, there is still a long way to go for a better understanding of the gut microbiota related to human immunity -

the vast majority of studies carried out in humans are correlational and do not allow us to understand with certainty whether intestinal dysbiosis precedes the disease or presents itself as a consequence of it.

In this sense, in this field, the use of antirheumatic drugs is a good example of how the mobilization of the intestinal microbiota and its imbalance can affect its functionality. We can mention, as an example, sulfasalazine, a drug used to treat inflammatory arthritis and ulcerative colitis, which relies on the enzymatic cleavage made by gut microbes.

THERAPEUTIC PERSPECTIVES

So far we have seen how the connection between the intestine and the brain is complex, involves several regions, parts of the human body and is capable of altering several vital functions, that is, a deep "dialogue" occurs between these regions. In this continuous "conversation" it is very important to remember a fundamental factor for its occurrence or change, the diet. Probiotics and prebiotics combined with a balanced diet become protagonists of this entire process, not only of intestinal health, but also of all modulation of mental and emotional state. Thus, this chapter will deal with a therapeutic universe exploring how their interactions act directly on the dynamics of the gut-brain axis, focusing mainly on the emotional and cognitive state.

At the outset, it is important to point out that the action of probiotics is highly studied all over the planet, with numerous researches carried out. Concomitantly, these studies demonstrate that the introduction of probiotic bacteria into the diet is able to raise the levels of neurotransmitters in brain tissues, and thus offers a kind of prevention of depressive treatments. In one of these studies, the presence of *Lactobacillus plantarum* (DP189) resulted in antidepressant effects in rats subjected to corticosterone-induced chronic stress. Effects that were circumvented from a 3-week period in which behavioral, histopathological, and biochemical improvements began to occur, including improved memory, special learning, and a reduction in anhedonia. In line with this study, another test carried out with strains of *L. plantarum* It showed similar results in healthy male mice, highlighting its antidepressant and anxiolytic effects. At biochemical levels, DP198 supplementation was responsible for reducing the numbers of apoptosis of neurons in the hippocampus.

In addition, the stress caused to these animals resulted in a lower number of neurotransmitters such as serotonin, dopamine and norepinephrine, a situation that was circumvented with the administration of the probiotic. These studies were also able to demonstrate that live probiotics are able to influence the gastrointestinal microbiota and modulate the immune response. Inactive probiotics, on the other hand, exert an anti-inflammatory role.

In addition to the strains taught in the previous studies, another strain known as *Bifidobacterium breve* (CCFM1025) when analyzed in mice on chronic stress, it was able, after a

period of five weeks, to significantly reduce behaviors related to anxiety and depression. Not only that, the strain helped attenuate inflammation caused by the high hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, since elevated serum corticosterone levels in these stressed animals were restored to normal.

Now moving on to human trials, a pilot study with ten patients diagnosed with major depressive disorders (MDD) without the influence of antidepressant medications underwent probiotic supplementation. This administration was responsible for a significant reduction in anxiety levels and overall improvements in the patients' mood as early as the fourth week of testing. In addition, there are also improvements in the anhedonia and sleep quality of each participant throughout the supplementation period.

Also in patients with major depressive disorders, it was possible to analyze the biochemical parameters when supplemented with *Lactobacillus plantarum* 299v (LP299v) that indicated a significant decrease in kynurenine concentration and improvements in cognitive functions in the LP299v group compared to the placebo group, which demonstrates a positive correlation between the use of probiotics and the enhancement of cognitive functions. Although serum levels of inflammatory cytokines remained unchanged in all groups, it was still possible to observe a reduction in symptoms of depression along with significant drops in urinary cortisol levels, which suggests positive effects of the probiotic in the regulation of physiological stress.

Along with patients with MDD, another strain, but this time with the *Bacillus coagulans* MTCC 5856 has also been tested in individuals with irritable bowel syndrome. The results remained the same, with a significant reduction in clinical symptoms of depression. In addition, positive effects of the strain were observed on sleep quality and decreased levels of myeloperoxidase, an enzyme involved in regulating the immune system. Thus, these findings highlight the therapeutic potential of probiotics in the context of the gut-brain axis, which paves the way for new approaches in the field of mental disorders.

Regarding the effects of prebiotics on depressive disorders, the literature is scarcer, with less testing and information regarding probiotics. However, it is still possible to find studies, such as treatment with fructooligosaccharides (FOS) in the relief of depression-like behaviors. In addition, in models of chronic stress caused by corticosterone induction (CUMS) in rats, the administration of FOS was able to restore elevated corticosterone levels, which demonstrates a normalization of the activity of the hypothalamic-pituitary-adrenal (HPA) axis. Not only that, the treatment also contributed to the restoration of the integrity of the intestinal epithelium compromised by the stress model. In addition to the treatment process with FOS, it is possible to understand that the administration of galacto-oligosaccharides (GOS) in male mice, induced to anxiety, during a period of three weeks was able to reduce the anxiety in the tests.

Such studies highlight that both treatment with fructooligosaccharides and galacto-oligosaccharides have the potential to exert antidepressant and anxiolytic effects, as well as significant changes in behavior and brain neurochemistry. Thus, it is possible to affirm great potential in therapeutic strategies in the maintenance of intestinal and brain health.

Moving back to human studies, the efficacy of the combined use of probiotics and prebiotics as complementary therapy in reducing depressive symptoms in a study conducted with 110 patients showed very promising results. All individuals with MDD were in three distinct groups. Two of them received probiotic supplementation, while the last received placebo for eight weeks. All supplementation groups showed a significant decrease in Beck Depression Inventory (BDI) scores compared to the placebo group. These findings underscore the potential of the symbiotic approach in the complementary treatment of depression, gaining a new therapeutic perspective in the context of the gut-brain axis.

As time and the scientific world advances, it becomes increasingly necessary to seek specific interventions aimed at modulating the intestinal microbiota and improving the immune system as the purpose of an increasingly better search for homeostasis. Thus, in order to encompass these two fields, new therapeutic perspectives are needed, such as the meta-analysis of clinical trials published by the journal "*Nutritional Neuroscience*" in 2021 that discerns about the reduction of cases and symptoms of depression by probiotic supplementation, the improvement of the effectiveness of traditional antidepressants through interventions directed at the gut microbiota according to a study published by the journal "*Psychological Medicine*" in 2020 and among other diverse literary studies.

However, to translate these findings into concrete clinical interventions, it is essential to understand other underlying mechanisms, such as the modulation of neurotransmitters from probiotics such as serotonin and gamma-aminobutyric acid (GABA) that are closely linked in mood and behavioral regulation.

This more detailed and deeper understanding of these mechanisms will allow the development of more accurate and truly effective therapeutic perspectives for the general population. Finally, research should continue to explore these specific interventions on how to modulate the microbiota, improve immune function, and the relationship with the central nervous system.

In the course of all the topics, it was possible to explore the complex and intrinsic world of the gut microbiota and all its comprehensive participation in human health. From the regulation of the immune system to the modulation of brain function, each bacterium that resides in the intestine plays a key role in a huge network of physiological processes.

The growing search for understanding this relationship between the microbiota and the entire immune process presents a new paradigm in medicine with numerous questions and future discoveries that are very important for human health. Today it is possible to understand that bacteria

not only aid in food digestion, but are also responsible for producing crucial metabolites that modulate the immune response and control inflammation. In addition, they directly influence the integrity of the blood-brain barrier, the production of neurotransmitters, which generate significant impacts on mood, brain function and in cases of depression.

Intestinal dysbiosis, which occurs due to an imbalance in the microbiota, emerges as a significant factor for the occurrence of crucial neurological diseases that are well known and have a great impact on the world population, from Parkinson's disease to multiple sclerosis. However, there is hope if this situation of imbalance occurs, since there are strategies that promote the balance of the microbiota again, as in the case of the use of probiotics, prebiotics and an adequate diet. Thus, there are opportunities to prevent and treat these debilitating conditions.

Therefore, it is of great importance that research on the gut-brain axis continues to explore new therapies and interventions that correlate the modulation of these two systems together. It is possible, by virtue of all that has been discussed throughout these four topics and the numerous researches mentioned, to say that one of the futures of medicine may lie in the ability to carefully manipulate these macrobiotic communities for the benefit of human health. May these topics serve as a guide to the understanding and powerful use of all this very rich ecosystem that resides within each human being, not only shaping each being, but also the life of each one.

REFERENCES

1. D'Amelio, P., & Sassi, F. (2018). Gut Microbiota, immune system, and bone. Calcified tissue international, 102(4), 415–425.

2. Hanssen, N. M. J., & Nieuwdorp, M. (2021). Interaction between the microbiome and the immune system. Nederlands tijdschrift voor geneeskunde, 164.

3. Hold, G. L., & Hansen, R. (2019). Impact of the gastrointestinal microbiome in health and disease: Co-evolution with the host immune system. Em: Current Topics in Microbiology and Immunology, 421, 303–318.

4. Mayer, E. A., Nance, K., & Chen, S. (2022). The gut–brain axis. Annual review of medicine, 73(1), 439–453.

5. Secombe, K. R., et al. (2019). The bidirectional interaction of the gut microbiome and the innate immune system: Implications for chemotherapy-induced gastrointestinal toxicity. International journal of cancer, 144(10), 2365–2376.

6. Zhao, Z., et al. (2021). Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis. Microbiome, 9(1).

7. Dinan, T. G., & Cryan, J. F. (2017). The microbiome-gut-brain axis in health and disease. Gastroenterology clinics of North America, 46(1), 77–89.

8. O'Mahony, S. M., et al. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural brain research, 277, 32–48.

9. Parker, A., Fonseca, S., & Carding, S. R. (2020). Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. Gut microbes, 11(2), 135–157.

10. Roth, W., et al. (2021). Tryptophan metabolism and gut-brain homeostasis. International journal of molecular sciences, 22(6), 2973.

11. Xie, J., et al. (2023). Gut microbiota regulates blood-cerebrospinal fluid barrier function and Aβ pathology. The EMBO journal, 42(17).

12. Zhu, S., et al. (2020). The progress of gut microbiome research related to brain disorders. Journal of neuroinflammation, 17(1).

13. Chudzik, A., et al. (2021). Probiotics, prebiotics and postbiotics on mitigation of depression symptoms: Modulation of the brain–gut–microbiome axis. Biomolecules, 11(7), 1000.

14. Liu, R. T., Walsh, R. F. L., & Sheehan, A. E. (2019). Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. Neuroscience and biobehavioral reviews, 102, 13–23.

15. Yadav, M. K., et al. (2022). Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics. Applied microbiology and biotechnology, 106(2), 505–521.

16. Buga, A. M., et al. (2023). The gut–brain axis as a therapeutic target in multiple sclerosis. Cells (Basel, Switzerland), 12(14), 1872.

17. Doroszkiewicz, J., Groblewska, M., & Mroczko, B. (2021). The role of gut Microbiota and gut–brain interplay in selected diseases of the central nervous system. International journal of molecular sciences, 22(18), 10028.

18. Manasson, J., Blank, R. B., & Scher, J. U. (2020). The microbiome in rheumatology: Where are we and where should we go? Annals of the rheumatic diseases, 79(6), 727–733.

19. Hsu, Y.-C., et al. (2023). Efficacy of probiotic supplements on brain-derived neurotrophic factor, inflammatory biomarkers, oxidative stress and cognitive function in patients with Alzheimer's dementia: A 12-week randomized, double-blind active-controlled study. Nutrients, 16(1), 16.

20. Tan, A. H., Lim, S. Y., & Lang, A. E. (2022). The microbiome–gut–brain axis in Parkinson disease — from basic research to the clinic. Nature reviews. Neurology, 18(8), 476–495.

21. Tansey, M. G., et al. (2022). Inflammation and immune dysfunction in Parkinson disease. Nature reviews. Immunology, 22(11), 657–673.