GUT MICROBIOTA AND ITS EFFECTS ON METABOLIC AND NEUROLOGICAL HEALTH

A MICROBIOTA INTESTINAL E SEUS EFEITOS NA SAÚDE METABÓLICA E NEUROLÓGICA

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ABSTRACT

The human gut microbiota plays various essential roles, including protection against pathogens, intestinal function regulation, synthesis of compounds for the host, diet compound metabolism, and direct influence on host homeostasis. The composition of the microbiota is influenced by factors like diet, age, and lifestyle, with the Westernized culture being associated with harmful imbalances. Disruption of the gut microbiota has been linked to various pathological processes, from intestinal syndromes to systemic conditions like allergies, insulin resistance, and neurological alterations. Microbiota disturbances can lead to cellular changes in colorectal tissue due to metabolic, genomic, and inflammatory influences. Therapeutic interventions to modulate the gut microbiota are considered promising approaches for managing and preventing these diseases. Continuous research on the gut microbiota and its relation to human health is of utmost importance to understand the underlying mechanisms and develop specific therapeutic interventions, complementing conventional treatment approaches.

KEYWORDS: Gut microbiota, Diabetes, Alzheimer's disease, Parkinson's disease, Cancer

RESUMO

A microbiota intestinal humana desempenha diversas funções essenciais, como a proteção contra patógenos, regulação da função intestinal, síntese de compostos a serem utilizados pelo hospedeiro, metabolismo de compostos da dieta, influenciando diretamente na homeostase do hospedeiro. A composição da microbiota é influenciada por fatores como dieta, idade e estilo de vida, sendo a cultura ocidentalizada associada a desequilíbrios prejudiciais. A disbiose da microbiota intestinal tem sido associada a diferentes processos patológicos, que vão desde síndromes intestinais a processos sistêmicos, como alergias, resistência à insulina e alterações neurológicas. Perturbações na microbiota intestinal podem

levar a alterações celulares no tecido colorretal, devido às influências metabólicas, genômicas e inflamatórias. Embora haja muito a ser compreendido, evidências indicam que intervenções terapêuticas para modular a microbiota intestinal podem representar uma abordagem promissora no manejo e prevenção dessas doenças. Portanto, a pesquisa contínua sobre a microbiota intestinal e sua relação com a saúde humana é de extrema importância para uma compreensão aprofundada dos mecanismos subjacentes e o desenvolvimento de intervenções terapêuticas específicas, impactando positivamente no tratamento e prevenção de várias doenças, complementando as abordagens convencionais de tratamento.
PALAVRAS-CHAVE: Microbiota intestinal, Diabetes, Doença de Alzheimer, Doença de Parkinson, Câncer.

INTRODUCTION

The human gut microbiota is recognized as the largest microecosystem present in the human body. This microbial community is extremely complex and heterogeneous, composed of bacteria, archaea, fungi, and viruses that interact with each other and the human host in a symbiotic manner[1,2]. While the stomach harbors only a few bacteria, the colon contains approximately 300 to 1000 different species, explaining why up to 60% of the dry mass of feces is made up of bacteria[3].

During parturition, the establishment of the gut microbiota begins, and although there is a lot of diversity in its composition among babies, a pattern can be identified with the initial colonization of facultative anaerobic microorganisms such as the genera *Bifidobacterium*, *Bacteroides*, and *Parabacteroides*[3]. On the other hand, in elderly individuals, aging affects the composition and functionality of the microbiota, as common changes in dietary habits (reduced salivary function, appetite, dentition, and digestion), physiological impacts of frequent medication use, or even gastric hypochlorhydria occur during this phase[4].

The gut microbiota plays a wide range of essential functions in the body, being fundamental for protection against pathogens as its presence on the mucosal surfaces results in the production of antimicrobial substances and competition for nutrients and adhesion sites. Additionally, the gut microbiota regulates the differentiation and proliferation of epithelial cells, influences insulin control, and

plays a crucial role in maintaining intestinal homeostasis. These interactions have significant implications in the etiology of various metabolic, cardiovascular, neurodegenerative, and neoplastic diseases[4,5].

The composition of the microbiota is influenced by various factors, including diet, age, genetic factors, and lifestyle[3]. It is essential to highlight that the Westernized culture has been identified as a negative factor for this microbial community, given its dietary pattern associated with inadequate intake of fruits and vegetables, excessive consumption of meats, saturated fats, sugars, and refined grains. These dietary habits have consistently shown damaging effects on the microbiota, emphasizing the importance of adopting a balanced and healthy approach to eating[4].

The disruption of the symbiosis between the human host and its microbiota can lead to negative consequences for both. This results in imbalances that increase the risk and exacerbate a variety of diseases, including cancer, diabetes, liver disease, Alzheimer's, and Parkinson's, among others. These conditions underscore the urgent need for more in-depth research to comprehensively understand this complex relationship. Advancing knowledge in this area is of utmost importance as it enables the development of effective strategies to promote health and prevent diseases associated with the microbiota. Therefore, the aim of this review is to investigate and describe how the gut microbiota influences the metabolic and neurological health of human beings[4].

RELATIONSHIP BETWEEN GUT MICROBIOTA AND DIABETES

Diabetes Mellitus (DM) is a group of metabolic diseases with multifactorial etiology and some distinctive features. The two most common types are Type 1 Diabetes Mellitus (DM1) and Type 2 Diabetes Mellitus (DM2). DM1 is autoimmune and characterized by deficiency or absence of insulin production by the pancreas. On the other hand, DM2 occurs due to the development of insulin resistance in cells, leading to a hyperglycemic condition, maintaining elevated circulating glucose, and compensatory hyperinsulinemia as a mechanism[6].

The gut microbiota, along with its metabolites, participates in the regulation of glucose sensitivity. Thus, there is a pattern of dysbiosis present in the host that can interfere with cellular insulin resistance (IR). Molecules and metabolites from the gut microbiota, such as lipopolysaccharides (LPS), secondary bile acids, and imidazole propionate, have been linked to the development of DM2, and their possible pathogenic mechanisms are being elucidated[7].

LPS is a component found in the outer membrane of Gram-negative bacteria and, when present in the host's bloodstream, can activate the immune system, being considered an endotoxin. LPS is recognized by TLR4 and CD14 receptors, stimulating the activation of the inflammatory signaling pathway NFκB, which leads to increased production of inflammatory factors such as TNFγ, IL1β, IL-6, and TNFα. As a result, the IRS (Insulin Receptor Substrate) is phosphorylated in an atypical manner, leading to insulin resistance[8] (Figure 1).

In addition to LPS, bile acids produced by the liver and secreted into the intestine can also affect insulin sensitivity if their metabolism becomes altered due to excessive conversion by the gut microbiota. Normally, primary bile acids are converted into secondary bile acids by intestinal microorganisms, which are responsible for synthesizing, modifying, and transducing signals in various processes, including glucose metabolism regulation. However, in excess, the binding of these molecules to the farnesoid X receptor (FXR) and tryptophan hydroxylase activating receptor (TGRS) stimulates the release of 5-hydroxytryptamine in chromaffin cells, resulting in reduced insulin release and increased glucagon secretion[9].

Another factor that may be associated with the development of insulin resistance in certain conditions is the chronic hyperactivation of mammalian target of rapamycin complex 1 (mTORC1). It is known that imidazole propionate, a product of histidine metabolism in the gut microbiota, can activate this complex and is found in higher concentrations in individuals with DM2[10,11]. Imidazole propionate impairs glucose tolerance, as it negatively affects insulin signaling at

the insulin substrate receptor through the activation of p38γ MAPK, a protein kinase signaling pathway. This activation results in the phosphorylation of p62 and, consequently, the activation of the mechanistic target of rapamycin complex 1 (mTORC1)[10] (Figure 1).

It is important to note that insulin resistance is a multifactorial condition and cannot be solely attributed to changes in the gut microbiota. Furthermore, more research is needed to fully understand the mechanisms involved between specific microbial strains and DM2. However, the evidence supporting the pro-inflammatory condition as a pathogenic contributor to insulin resistance and DM2 is growing stronger[6].

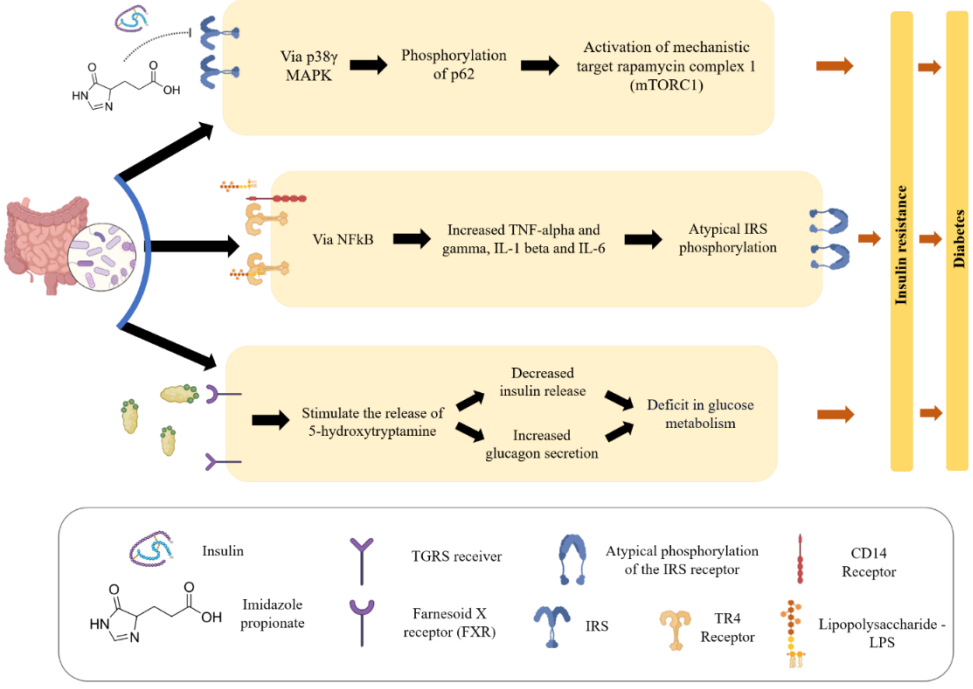

Figure 1. Mechanisms by which dysbiosis results in diabetes.

THE GUT-BRAIN AXIS

There is a bidirectional communication between the gut and the brain known as the gut-brain axis, involving various systems such as the central nervous, endocrine, and immune systems. The dysregulation of brain activity and

cognitive functions is triggered by an imbalance in the gut microbiota[12]. This dysbiosis is directly associated with several psychiatric disorders such as anxiety, depression, epilepsy, autism spectrum disorder, as well as neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD)[12,13] (Figure 2).

The interactions between the gut-brain axis occur through the production, transport, and functioning of neurotransmitters or their precursors, as well as short-chain fatty acids produced by the gut microbiota, which are active metabolites. These metabolites also act in the local nervous system, such as the vagus nerve, enteric nerves, and neuroendocrine cells located in the intestinal epithelium. In addition to the classic hypothalamic-pituitary-adrenal axis and its endocrine pathways, these interactions can also involve enteroendocrine cells or the gut microbiota itself[12].

The availability of these metabolites and neurotrophic factors, which are produced, depends directly on the symbiotic metabolism of the gut microbiota, activated by certain bacterial taxa present in some species of bacteria[12,14]. Some neurotransmitters involved in this axis can be excitatory, such as glutamate, acetylcholine, and dopamine, while others are inhibitory, such as gamma-aminobutyric acid (GABA), glycine, and serotonin. Other components, like norepinephrine, tyramine, phenylethylamine, and tryptamine, can also act as neurotransmitters in this process. The imbalance in these neurotransmitters can lead to neurological and even psychiatric disorders[12].

The presence of neurodegenerative diseases such as AD and PD is accompanied by gastrointestinal disturbances, indicating that the pathologies themselves bring about dysbiosis and have a relationship with the regulation of the gut microbiota[15]. Although Alzheimer's and Parkinson's have different etiologies and mechanisms, they exhibit several overlapping symptoms and characteristics[13].

THE ASSOCIATION OF GUT MICROBIOTA AND ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive, neurodegenerative, and irreversible condition of significant importance to global public health. Its etiology is complex and varied, and it may be associated with the gut microbiota, which exhibits considerable variation from one individual to another. This diversity makes it challenging to pinpoint a specific cause, given its multifaceted nature. In the gut microbiota, certain bacteria and/or their metabolites interact with the intestinal epithelium, either favoring the future onset of the disease or antagonistically contributing to its prevention through early diagnosis. By understanding the relationship between gut microbiota and the brain and studying the metabolites produced through this interaction, it is possible to identify promising biomarkers for the early detection of Alzheimer's disease. For instance, measuring levels of Aβ (beta-amyloid) in blood plasma and investigating the presence of cerebral amyloidosis can serve as early indicators of this neurodegenerative disease[16,17].

The connection between the onset of AD and gut microbiota can be explained by disruptions in the epithelial integrity of gap junctions present in the intestines. Changes in gut microbiota, dysbiosis, or increased intestinal barrier permeability may lead to the translocation of microorganisms and endotoxins into the bloodstream, resulting in a generalized inflammatory response. Over time, this inflammation can progress to chronic neuroinflammation[18,19]. Several studies provide evidence of a relationship between the brain-gut axis and the development of AD through the gut microbiota. This relationship is associated with neuroinflammation resulting from dysregulation of the tryptophan metabolism pathway, which is produced in the gut along with its metabolites. It is essential to highlight that tryptophan and its metabolites play a crucial role in neuroplasticity and energy production when present in appropriate quantities. However, in excess, these substances produce neurotoxic and pro-inflammatory by-products, contributing to chronic neuroinflammation[20].

Short-chain fatty acids, byproducts of fermentation carried out by intestinal bacteria, act to inhibit pro-inflammatory factors. These fatty acids can be

obtained through probiotics and already show beneficial impact on serum levels of BDNF (Brain-Derived Neurotrophic Factor), improving neuronal functions. Clinical studies employing biochemical tests (plasma Aβ levels and serum BDNF), cognitive assessments (Alzheimer's Test, memory and learning questionnaires), genetic coding and sequencing (microbiome analysis and genetic replication), stress, and mood (BDNF) demonstrate positive outcomes in the early improvement of function, cognition, learning, and memory related to dementia. However, the dosing of probiotics and strains varies from one experiment to another, and a definitive causal relationship between probiotics and neurodegeneration has not yet been established[21].

THE GUT MICROBIOTA IN PARKINSON'S DISEASE

Parkinson's Disease is known as a movement disorder characterized by muscular rigidity, postural instability, gait disturbances, bradykinesia, and resting tremors. However, it is common for patients to present with other symptoms, including cognitive impairments and gastrointestinal symptoms, which can precede motor symptoms by up to 20 years[22,23].

In an effort to understand the effects of the gut microbiota on PD, some results indicate a decrease in bacterial phylogenetic diversity and β-diversity of the gut microbiota. High levels of *Akkermansia* have been reported in the intestines of PD patients, which can lead to colonic mucus degradation, increased susceptibility to pathogens, and increased intestinal permeability, resulting in local inflammation. Since high levels of the bacterium *Akkermansia* are negatively associated with NOD-like receptor family pyrin domain containing 6 (NLRP6), its absence leads to impaired IL-18 production, resulting in increased susceptibility and induced epithelial injuries[24].

Metabolic studies demonstrate an increase in the population of *Akkermansia* and *Bifidobacterium* and a decrease in *Faecalibacterium* and *Lachnospiraceae* in PD patients. Changes in stool firmness are observed in PD patients due to slow colonic transit caused by constipation, favoring the growth of

bacteria with slower growth rates, as well as being associated with reduced nutrient availability. Currently, the recommended treatment is a combination of probiotics with prebiotic fiber. Slow colonic transit causes changes in the metabolism of the gut microbiota, shifting away from carbohydrate fermentation and towards proteolysis. The levels of P-cresol and phenylacetylglutamine are elevated in PD and correlate with firmer stools and severity of constipation. Several taxa are associated with chronic constipation in PD patients: *Dorea, Oscillospira, Ruminococcus*, and cluster B are positively associated with constipation, while *Faecalibacterium* and total butyrate producers are negatively associated with constipation[25].

New evidence indicates that the gut microbiota producing short-chain fatty acids (SCFAs) is less abundant in association with the severity of PD, which may lead to rapid motor and cognitive deterioration. Butyric acid is related to cognitive decline in patients, causing increased intestinal permeability and intestinal inflammation, leading to disease aggravation[26].

THE INFLUENCE OF GUT MICROBIOTA ON CANCER

Cancer can arise from chronic infections, as they trigger immune responses with pro-inflammatory characteristics that cannot eliminate the infection and contribute to cellular disarray. As mentioned earlier, disturbances in the gut microbiota can result in an exacerbated inflammatory response, contributing to tumor formation. Currently, the contribution of eubiosis to the effectiveness of therapeutic approaches and the prognosis of different tumors, especially colorectal cancer, has been observed[27,28].

Colorectal cancer is the second leading cause of cancer-related death worldwide in both sexes. The intestines harbor numerous bacteria, and disturbances in this microbial community can lead to cellular changes in the colorectal tissue, as the microbiota interferes with metabolic, genomic, and inflammatory characteristics. Thus, combinations of different probiotics can be

used to reduce inflammatory responses related to tumor formation, aiming to restore intestinal functions through the remodeling of the gut microbiota[29,30].

The modulations enabled by eubiosis contribute to the therapeutic aspect for controlling this type of cancer. There is evidence that therapeutic interventions, such as chemotherapy, alter the gut microbiota, which may be associated with tumor recurrences and side effects during treatment. A prospective randomized study administering probiotics from the third day after colorectal surgery until the end of the first cycle of chemotherapy resulted in fewer cases of reactive-type diarrhea. Therefore, the rebalancing of the microbiota facilitated by probiotics may reduce the gastrointestinal effects caused by chemotherapy[30].

Although studies linking gut microbiota and cancers outside the digestive system are limited, some research indicates that the microbiota influences the immune control of cancers, such as melanoma. Currently, disparate therapies are available as alternatives to controlling tumor formation. However, these therapies are not yet entirely effective, leading to the development of interventions based on immunotherapy for controlling this pathology. Immune checkpoint inhibition (ICI) is a type of immunotherapy targeted for improvement and used in different types of cancer, especially melanoma. This ICI affects immune cells in different tissues, including immune cells lining the intestinal mucosa, which is influenced by the microorganisms present in the gut. The interaction between the immune system and the gut microbiota can affect the outcomes of immunotherapies depending on the stability of the gut microbiota[28].

Currently, there is an increasing number of studies establishing the relationship of the gut microbial community with the lungs. If these bacteria are not eliminated by the immune system, they can reach the mesenteric lymphatic system, enter the circulatory system, and subsequently reach the pulmonary circulation, activating antigen-presenting cells. With the activation of these cells, it is possible to trigger an effective immune response and contribute to the suppression of the pulmonary tumor environment[27].

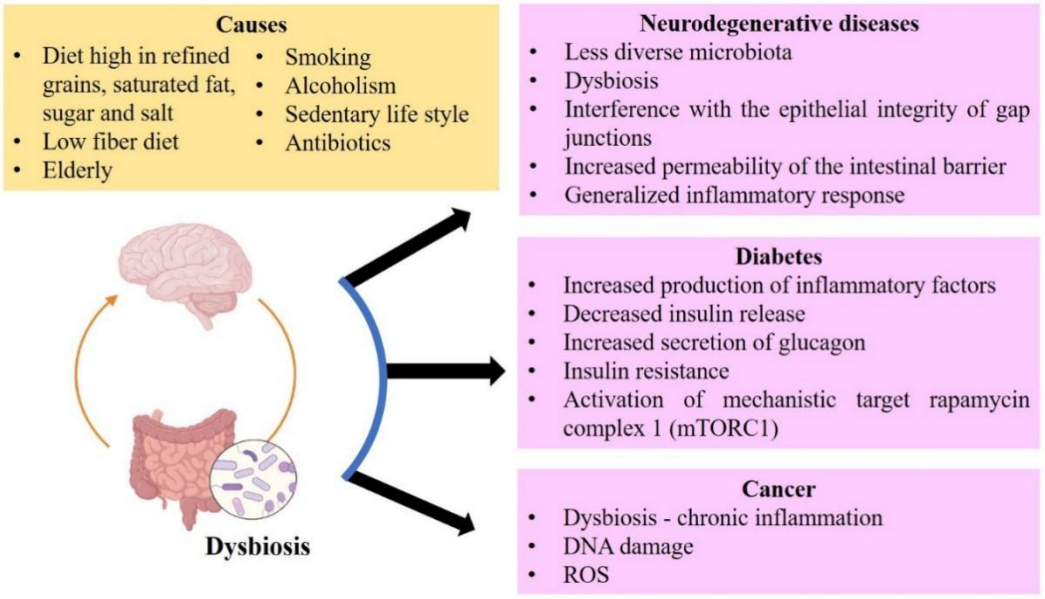

Figure 2. Causes and effects of dysbiosis.

CONCLUSION

The number of research studies on the human gut microbiota has grown in recent years due to discoveries about its influence on the host's metabolism, physiology, and immune system. Although there is still much to be understood, evidence suggests that therapeutic modulations of the gut microbiota may represent a promising approach in the management and prevention of these diseases. Therefore, continuous studies on the gut microbiota and its relationship with human health are of utmost importance for a better understanding of the underlying mechanisms and to develop specific therapeutic interventions, positively impacting the treatment and prevention of various diseases with promising and complementary approaches to conventional treatments.

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