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REVIEW ARTICLE

Human gut microbiota and Parkinson's disease

Microbiota intestinal humana y enfermedad de Parkinson

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Abstract

The gut microbiota and its activity are directly or indirectly linked to different functions in the human body. Interactions between intestinal microorganisms and the CNS have been described through the microbiota-gut-brain axis. Currently, the role of this interaction is under study to understand its impact on Parkinson's disease. To settle a base and then identify questions yet to be answered, we performed a directed search of literature is carried out in search engines and virtual libraries such as PubMed, ResearchGate, GoogleScholar, UNAM Information Discoverer, etc., using keywords such as "microbiota","human gut microbiota","gut-brain- axis" and "Parkinson's Disease", and the articles that will touch on these topics are selected from their summary. We concluded that current scientific literature let us know that intestinal microbiota has an active role in the pathogenesis of Parkinson's disease and many mechanisms have been proposed and studied. However, the impact of these mechanisms on the genesis of Parkinson's disease is still unknown.

Keywords: *Parkinson's Disease. Microbiota. Human Gut Microbiota. Microbiota-Gut-Brain Axis.*

Resumen

La microbiota intestinal y su actividad están directa o indirectamente relacionadas con diferentes funciones en el cuerpo humano. Las interacciones entre los microorganismos intestinales y el SNC se han descrito a través del eje microbiota-intestino-cerebro. Actualmente, el papel de esta interacción está bajo estudio para comprender su impacto en la enfermedad de Parkinson. Para establecer una base y luego identificar preguntas aún por responder, realizamos una búsqueda dirigida de literatura en buscadores y bibliotecas virtuales como PubMed, ResearchGate, GoogleScholar, UNAM Information Discoverer, etc., utilizando palabras clave como "microbiota","microbiota intestinal humana","eje intestino-cerebro" y "enfermedad de Parkinson", y los artículos que tocarán estos temas se seleccionan de su resumen. Concluimos que la literatura científica actual nos permite saber que la microbiota intestinal tiene un papel activo en la patogénesis de la enfermedad de Parkinson y se han propuesto y estudiado muchos mecanismos. Sin embargo, el impacto de estos mecanismos en la génesis de la enfermedad de Parkinson es aún desconocido.

Palabras clave: *Enfermedad de Parkinson. Microbiota. Microbiota intestinal humana. Eje microbiota-intestino-cerebro.*

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Introduction

The human species have evolved along with different microorganisms. Some of them with pathogenic characteristics, but also in symbiosis with many other species. A large number of microorganism colonies live in healthy human bodies, all over the skin surface and inside cavities, but in this issue we will only discuss microorganisms that coexist inside the human gut and its relation with neurodegenerative diseases, especially Parkinson's Disease (PD). For further understanding of "healthy" microbiomes, we recommend reading about The Human Microbiome Project work[1,2].

Microbiota-gut-brain axis: the basics and its implication in neurologic conditions.

Our understanding of the communication between brain and gut comes from studies about peptides that are common between brain cells and gut cells[3], where the term "gut-brain axis" started to become popular. Most of those articles were published around the 80s. It wasn´t until the first years of the 21st century that the idea of "microbiota-gut-brain axis" (also known as "gut microbiota-brain axis" or "microbiome-gut-brain axis" when the microbe genes are took in count) took relevance and attention in the scientific literature[4]. This term is broadly used in the literature to explain the complex system of bidirectional communication between the brain and gut microbiome, which has been described in multiple species of vertebrates, including farm animals[5]. Human gut microbiota reside mainly in the colon and are composed of fungi, virus, bacteria and archaea, but most of the information comes from bacterial studies, with *Bacterioides* and *Firmicutes* as the most common bacterial phyla[6]. The bacterial communities that live in the human gut are capable of synthesize multiple neuroactive compounds, such as serotonin (5-HT), glycine, γ-aminobutyric acid (GABA), catecholamines and short chain fatty acids (SCFA)[7], which can modify and regulate the enteric nervous system, with consequent communication to the central nervous system (CNS)[8]. Among all communication pathways described, the vagus nerve is the most studied [7]. Vagus nerve can indirectly communicate with gut bacteria, sensing the compounds that diffuse across the epithelial layer through their interaction with gut endocrine cells, or directly, as in the direct activation of vagal afferent fibers with SCFA produced by bacteria[9]. The effect of vagotomy in the microbiota-gut-brain axis function is elsewhere reviewed[10]. There is abundant information about microbiome composition and dysbiosis associated with multiple neurological and neuropsychiatric conditions. The information regarding gut microbiota and Parkinson's Disease (PD) will be discussed later in this issue. Jiang et al. described differences between fecal microbiota in patients with depression and healthy subjects[11], which is replicated in multiple studies summarized in a systematic review by Knudsen et al.[12]. Probiotic supplementation[13-15] has been studied as a therapy in depression, with promising results. Some authors have described differences in gut microbiota of patients with epilepsy compared with healthy subjects[16,17]. Probiotics might be a supplementary therapy in patients with epilepsy, as Gomez-Eguílaz, et al. concluded in a pilot study[18]. Although some authors propose this therapy as an option for migraine patients[19], the current available information is limited and controversial[20,21].

The role of gut microbiome in pd

Microbiota composition in patients with PD

Microbiota composition is affected by host factors (age, sex, weight, etc) and environmental factors (geography, toxin and drug exposure, diet, etc), which make it difficult to reproduce results between population studies, but there are some highlights. In a nonparametric meta-analysis of intestinal microbiota in PD[22], Hirayama and Ohno found that *Akkermansia* is increased, and SCFA-producing bacteria are decreased in PD. Another meta-analysis conducted by Toh et al. found increased abundance of *Akkermansia* and *Megasphaera*, as well as decreased *Roseburia,* and bacterial genera correlated to motor symptoms severity[23]. Differences between gut microbiota of patients with PD with "stable disease" and those with faster progression has also been described[24], as well as differences between patients with idiopathic rapid eye movement sleep disorder (prodrome of PD) and healthy subjects[25]

Neurotransmitters synthesis and regulation by gut microbiome Dopamine

Dopamine

A variety of microbes have a direct or indirect impact on bioavailability of dopamine in the SNC[26], which may have a role in the pathophysiology of PD. Some strains of *Enterococcus* and *Lactobacillus* are cable to metabolize L-dopa to dopamine[27]. Wang et al. found that the administration of *E. faecalis* and *E. faecium* to PD mice increased the striatal dopamine[28]. On this basis, some authors suggest that these strains may be used as

probiotics due to their potential to synthesize dopamine (Hamamah et al., 2022)[26]. Another species of interest is *Ruminococcus*, a genus of the phylum *Firmicutes* that has shown negative influence in D2 receptor gene expression[29]. *E. coli* K12 can also synthesize dopamine, DOPA and in sufficient concentrations to human receptors to bind them (Shishov et al., 2009)[30].

Serotonin

Despite it's importance in neurological function and diseases, most of the serotonin in the human body is located in the gut[31]. It is known that some microbes promote and regulate serotonin synthesis in animal models as well as in humans, although the exact process they use is not fully elucidated[32]. One of the perhaps most accepted theories is the involvement of this bacteria in the kynurenine pathway and tryptophan metabolism on the gut and it's impact in peripheral and central serotonin activity[33]. Diverse studies suggest that plasma serotonin level is linked to microbe interaction[34] and this is important in PD because low serum levels of serotonin are associated with depression and pain in those patients[35].

Dysbiosis, inflammation and alpha-synuclein (α-Syn)

Abnormal α-Syn accumulation and aggregation is the pathologic hallmark of PD[36]. Nonetheless, it is yet in debate if this phenomenon is the cause of the disease or a consequence of an unknown primary process. Aside from this debate, the evidence of gut microbiota playing a role in intestinal inflammation and local α-Syn accumulation is abundant. This is important to take into account because there is evidence that directly links intestinal inflammation to the pathogenic process in PD[37]. Pro-inflammatory cytokines and chemokines can be measured in both colonic biopsies and stool samples of PD patients[38]. Keshavarzian et al. compared sigmoid mucosal biopsies and fecal samples of PD patients with healthy controls and reported increased pro-inflammatory bacteria of the genus *Ralstonia* in PD patients samples, as well as decreased abundance of *Blautia*, *Coprococcus* and *Roseburia* when compared to healthy controls[39]. *Roseburia* genera is known to express immunomodulatory activity through gene upregulation in the host[40]. Intestinal α-Syn in PD patients is correlated to inflammation and loss of gut integrity driven by microbial changes[38]. Animal model studies show that microbiota is required for α-Syn pathology (Sampson et al.) and when mice intestine is colonized with microbiota of human PD patients, motor symptoms are enhanced[41]. Braak et al. hypothesized that an unidentified agent would be able to pass the mucosal barrier in the gut and then travel retrogradely to the CNS, involving initially the dorsal motor nucleus of the vagus nerve (along with the olfactory bulb and anterior olfactory nucleus) and the spreading to the rest of the brain in a proposed specific fashion that correlates with the clinical progressión in PD[42]. The initial phenomena proposed in the so called Braak's hypothesis is consistent with animal model experiments showing the propagation of pathologic α-Syn from the gut to brain through the vagus nerve and then causing PD in mice[43]. In this same study, Kim et al. observed that truncal vagotomy prevented the propagation of α-Syn from gut to CNS after injection of this protein in mice gut[43].

Interactions between anti-parkinsonian drugs and gut microbiome

Human gut microbiota is known to influence the absorption and metabolism of oral drugs by enzyme activity, alteration in drug transport and changes of gastrointestinal properties (Zhang et al. 2021)[44]. *E. faecalis* is capable of metabolizing levodopa (L-dopa) by decarboxylation, as Rekdal VM et al. described[45]. The use of L-dopa induces tyrosine decarboxylase gene expression in gut bacteria, which has implications in PD drugs bioavailability[46]. Some authors have hypothesized that microbiota may be implicated in the presence of adverse effects associated to entacapone[47].

Microbiota-gut-brain axis as a target in PD treatment and prevention

Probiotics

Despite the evidence being limited, there are some efforts to study probiotic supplementation as a therapy in PD. A meta-analysis that included 663 subjects from 9 randomized controlled trials (RCT) found that oral probiotic supplementation might improve motor and non-motor symptoms in PD[48]. Nonetheless, the authors declared the evidence is inadequate and limited. Probiotics intake may be useful to treat constipation in PD[49,50], however bigger and longer RCT are needed to ensure safety and efficacy over the time[50,51]. Probiotics may improve mild cognitive symptoms in PD and Alzheimer's Disease, as another meta-analysis suggests[52]. Tamtaji et al. found in a RCT an overall

improvement in the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in patients receiving probiotics when compared to placebo[53], but they did not specify which domains improved.

Diet

The Mediterranean diet (MeDi) is probably the most studied in the field of neurological diseases, especially in the scenario of vascular disease prevention. The adherence to MeDi may reduce the risk of PD and AD[54], but the role of gut microbial changes in this outcome is yet to be proven. Olive oil (a main component of MeDi) and Koroneiki extracts (*Olea europaea*) have shown to reduce α-Syn aggregation in *in vivo* studies[55]. Both low-fat diet and ketogenic diet (KeDi) can improve motor and non-motor symptoms of PD[56]. In addition, KeDi seems to be effective in reducing cognitive symptoms in PD and AD[57].

Vagal interventions (vagotomy/vagal stimulation)

As previously mentioned, the vagus nerve plays a preponderant role in the microbiota-gut–brain axis as a pathway for neuroactive and pathogenic compounds (such as α-Syn) to travel from gut to the CNS. This has led to interesting hypotheses and proposals. For example, in a Swedish cohort of 9430 vagotomized patients, Liu et al. found evidence suggesting that truncal vagotomy is related to a lower risk of PD[58]. Another cohort in Denmark found similar results[59]. Vagal nerve stimulation (VNS) seems to have neuroprotective effects in PD animal models[60], but evidence of this phenomenon in humans is yet lacking. Nonetheless, it has been studied as a therapeutic tool for PD motor symptoms with limited but interesting evidence[61].

Conclusions and future perspectives

The idea of PD being an isolated CNS disease is outdated. Even though the cause (or causes) is not known, there are multiple hypotheses that try to explain the genesis of this degenerative disease. Recently, gut microbiota has gained attention among the scientific community, especially in neurosciences, and this has led to a wave of literature assessing these issues.

Is clear that gut microbiota has an active role in the pathogenesis of PD and multiple mechanisms have been proposed and tested, from synthesis and modulation in neurotransmitters and other neuroactive molecules, to their participation in α-Syn synthesis in the gut. Nonetheless, the real impact of all these mechanisms in the genesis of the disease is not well established and it is improbable that it explains all the cases of PD.

However, treating the dysbiosis in PD patients seems to be a promising therapeutic target to treat or at least relieve some motor and non-motor symptoms of the disease and if we zoom out and address the gut-brain axis as a therapeutic target the fan becomes wider. There are some interesting questions yet to be answered in this specific topic. Which genera are the ideal for therapeutic use in the field of probiotic supplementation? Is the response the same in those patients with well documented dysbiosis compared to "normal microbiota" carriers? Could FMT be a therapeutic tool in these patients? On the other hand, bigger questions should be answered in the future: Gut bacteria is related to the genesis of the disease? If there is a specific genera of risk, does this mean that the risk might be transmitted from human to human? What is the real impact of truncal vagotomy in the prevention of the disease? and which patients may benefit from this intervention?

A lot of time and effort is needed to answer these questions, and this theory must be dealt with tweezers, as this is not the first time that a new hypothesis gets this much attention but yet none of the previous ones has proven to be the final answer and as far as we know, there might not be a unique answer that explains all the cases of the PD spectrum.

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