Gut microbiota: a potential therapeutic target for Parkinson's disease

José Fidel Baizabal-Carvallo*

Parkinson's disease (PD) is a neurodegenerative disorder characterized by accumulation of α-synuclein in neurons of the central nervous system (CNS). The pathogenesis of PD is complex and only partially understood. Initial evidence pointed to the basal ganglia as the source of the motor manifestations of PD, and likely the origin of the pathological process. In the last two decades, Braak and colleagues have drawn attention to the presence of α-synuclein in the nuclei of lower cranial nerves, suggesting that such protein was transported from somewhere in the gut. This finding started shifting the focus from the CNS to the gut in search for a pathogenic explanation for PD. Further pathological studies confirmed the presence of aggregated α-synuclein in the gut of individuals with PD. However, later observations showed that such abnormality was also present in some individuals without PD. These observations suggested that α-synuclein aggregates may be related to an infectious agent affecting the gut epithelia. In this scenario, gut microbiota may contribute to aggregation of α-synuclein. Emerging evidence has shown that protein nucleation and aggregation may be influenced by an extracellular amyloid protein called "curli", secreted by *E Coli*. Indeed, repeated administration of curli-producing bacteria to *Caenorhabditis elegans* and rats has induced neuronal deposition of α-synuclein in their gut and CNS promoting local inflammation (Chen et al., 2016).

In recent years, studies have shown that patients with PD have abnormal gut microbiota, a process known as dysbiosis. Although there is variability in the proportion of affected phyla, families, genera and species of gut bacteria among studies, an increase in Gram-negative bacteria seems to be a consistent finding. The origin of such dysbiosis is unclear; however, the influence of dietary habits, genetic background, chronic stress, abnormalities in gut motility, exposure to external toxins and certain bacteriophage virus have been suggested to play a role (Baizabal-Carvallo and Alonso-Juarez, 2020).

Evidence from histopathology and functional studies indicates that patients with PD also have increased gut permeability, allowing an enhanced translocation of bacteria and bacterial products such as lipopolysaccharides (LPS) to the systemic circulation. Such hyper-permeability state seems to affect mainly the colon and has been identified by observing an increased amount of bacteria in the epithelium and lamina propria of the sigmoid in patients with PD (Forsyth et al., 2011). Decreased expression of the protein occludin (a component of intercellular tight-junctions of colonic enterocytes) has been detected in patients with PD, compared to normal controls (Clairembault et al., 2015). Other observations including: abnormalities in functional studies of intestinal permeability, decreased serum levels of LPS binding protein and altered blood microbiome in patients with PD compared to controls add evidence supporting the presence of an abnormal intestinal permeability in PD, a condition known as "leaky gut" syndrome (Baizabal-Carvallo and Alonso-Juarez, 2020). Abnormalities in gut microbiota may lead to deficient production of butyrate, a short-chain fatty acid implicated in the proper function of intercellular tight junctions. Experimental cellular models have shown that butyrate decreases bacterial translocation by modifying the expression of intercellular proteins: claudin1 and claudin2, favoring the integrity of the intestinal barrier (Forsyth et al., 2011). Butyrate also has an anti-inflammatory effect, by reducing the intestinal production of tumor necrosis factor-alpha (TNF-α). Patients with PD have shown reduced fecal excretion of short-chain fatty acid and less abundant butyrate-producing bacteria compared to healthy controls (Keshavarzian et al., 2015). Few studies have addressed whether there is a change in gut microbiota over the years in patients with PD; however, it has been shown that lower counts of Bifidobacterium, Bacteroides fragilis and Clostridium leptium at baseline along with accelerated decrease of these bacteria overtime were associated with progressive worsening of motor and non-motor symptoms in patients with PD.

LPS, an endotoxin produced by Gram-negative bacteria residing in the intestines, can potentially translocate and reach the systemic circulation and the CNS. LPS has shown to activate brain microglia by binding to toll-like receptor type-4, leading to expression of a pro-inflammatory microglial profile with release of reactive oxygen species and inflammatory mediators, increasing the damage to dopaminergic neurons in the substantia nigra. Entrance of LPS into the CNS may be facilitated by dysfunction of the blood-brain barrier, an abnormality corroborated *in vivo* in patients with PD by means of functional neuroimaging (Baizabal-Carvallo and Alonso-Juarez, 2020). Furthermore, LPS seems to increase nitration and oligomerization of α-synuclein by local induction of the enzyme nitric oxide synthase (Choi et al., 2010). This evidence supports the notion that LPS not only enhances the inflammatory response of the CNS in patients with PD, but it could also accelerate the neurodegenerative process (Baizabal-Carvallo and Alonso-Juarez, 2020). Interestingly, increased population of LPS-producing bacteria was obtained from the gut mucosa and fecal samples of patients with PD compared with normal controls (Keshavarzian et al., 2015).

A systemic inflammatory response with increased levels of pro- and anti-inflammatory cytokines has also been identified in patients with PD. The origin of such immunological response is unclear; but it may be related to gut inflammation and dysbiosis. For example, one study showed that the abundance of LPS-producing bacteria, correlated with the plasma levels of TNF-α in Taiwanese patients with PD (Lin et al., 2019). This finding is connected with the observation that low levels of LPS binding protein enhance the activity of peripheral mononuclear cells leading to an increase in the synthesis and release of TNF-α.

It is unclear whether an abnormal microbiota may contribute to worsening of motor symptoms in PD. Enterobacteriaceae abundance correlated with postural instability and gait difficulties in one study (Sheperjans et al., 2015); whereas higher severity of motor symptoms correlated with the abundance of *Bacteroides* in another study (Lin et al., 2019). Most studies have not reported a correlation between motor function and abnormalities of gut microbiota. However, experiments in animal models have linked dyskinesia with neuro-inflammation; and the latter is enhanced by exposure to bacterial endotoxins. Abnormalities in gut microbiota may play a role in enhanced serum levels of TNF-α, which may strengthen the synaptic transmission in the CNS, contributing to the maladaptative plasticity registered in the striatum of patients with PD and levodopa-induced dyskinesia. Intestinal bacterial overgrowth (IBO), a form of dysbiosis, is a common finding in patients with PD. In a study of Chinese patients with PD, those with motor fluctuations had a higher proportion of IBO (71% *vs.* 46%) compared to PD patients without motor fluctuations (Niu et al., 2016). Microbiota

is also involved in the metabolism of levodopa. Recent evidence has implicated *Enterococcus faecalis* with a conserved tyrosine decarboxylase able to metabolize levodopa (Rekdal et al., 2019). This enzyme may accelerate levodopa metabolism in the gut decreasing its efficacy by a premature conversion to dopamine. If such enzyme is highly expressed in a dysbiotic gut, an incomplete response to levodopa would be expected promoting motor fluctuations. This evidence suggests that gut microbiota may influence the motor symptoms of PD, but more studies are necessary to confirm this preliminary finding.

Treatment: If an altered microbiota contributes to neuro-degeneration and worsening of motor symptoms in patients with PD, a therapeutic approach with the aim to reestablish a healthy microbiota would be desirable. Several strategies have been proposed to achieve this objective; including: (1) diet modifications; (2) the administration of probiotic bacteria in order to displace pathogenic bacteria; (3) the use of prebiotics, (nutrients metabolized by probiotic bacteria with the aim to accelerate bacterial growth); and (4) the use of synbiotics (combination of probiotics and prebiotics) (Gagliardi et al., 2018). The aim of these therapies would be to decrease the population of endotoxin-producing bacteria and increase the population of butyrate-producing bacteria in order to decrease systemic and neuro-inflammation. These strategies have proven effective in some gastrointestinal disorders with prominent gut inflammation. Experimental approaches such as fecal transplantation, bacterial consortium transplantation, bacteriophage therapy and the use of predatory bacteria have also been used to decrease gut inflammation, but experience is limited (Gagliardi et al., 2018). Treatment of IBO should also be considered in patients with PD. A short course of antibiotics is indicated to decrease bacterial population in the small intestine. Several agents have been used, including: tetracycline, neomycin, metronidazole, norfloxacin, ciprofloxacin, amoxicillin and rifaximin among others; the latter is widely used as it can eradicate small intestinal bacteria overgrowth in up to 80% of patients. Recommended doses of rifaximin vary between 600 and 1600 mg per day. Nutritional support is advocated when IBO is associated with malnutrition.

The use of certain strategies to reestablish a normal gut microbiota may be adjusted depending on the underlying disequilibrium in gut bacteria. For example, patients with the so-called "deficiency dysbiosis" resulting from unhealthy diets or chronic antibiotic therapy may benefit from the introduction of *Lactobacilli* and/or *Bifidobacterium*; whereas patients with "putrefactive dysbiosis", resulting from diets poor in fiber but rich in fat and meat have increased abundance of Bacteroides and IBO in the small intestine; these patients may benefit from short courses of luminal antibiotics and probiotics (Gagliardi et al., 2018). Patients with PD may have both types of dysbiotic conditions. The challenge when using therapeutic approaches to reestablish a normal microbiota in patients with PD would be to define the best clinical and biological markers to assess the impact of these therapies. As dysbiosis is potentially implicated in systemic and CNS inflammation in PD; a change in inflammatory markers would be a reasonable approach. Follow-up with validated clinical scales is desirable, although it is unclear for how long patients should be assessed; moreover, defining a clinical significant benefit may be complicated.

If therapeutic manipulation of gut microbiota proves effective to treat some pathogenic aspects of PD, an important inquiry would be at which point of the disease evolution these therapies should be implemented. It is accepted that microbiota conformation is shaped early in life with relative minor changes later on. However, patients with rapid eye movement-sleep behavior disorder (a condition that may precede the motor manifestations of PD) have shown gut microbiomes similar to those seen in patients with PD, but different to healthy controls (Heintz-Buschart et al., 2018), suggesting that dysbiosis may start very early within the evolution of PD; leading to the idea that interventions to modify gut microbiota may be implemented even in the premotor phase of the disease.

Concluding remarks: In conclusion, patients with PD frequently show abnormal populations of different intestinal bacteria, a state known as dysbiosis. Current evidence suggests that abnormalities in gut microbiota may contribute to neuro-inflammation and motor progression of PD. Further studies should clarify how such dysbiosis is implicated in the pathogenesis of this disorder, as implementing strategies to reestablish a normal microbiota would be desirable, possibly, even in the early phases of the disease.

José Fidel Baizabal-Carvallo*
Department of Science and Engineering, University of Guanajuato, Guanajuato, México
***Correspondence to:** José Fidel Baizabal-Carvallo, MD, MSc, baizabaljf@hotmail.com.
https://orcid.org/0000-0002-8614-5563 (José Fidel Baizabal-Carvallo)
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