



## Progress in Brain Research

Volume 252, 2020, Pages 357-450

---

Chapter 11 - The gut microbiome in Parkinson's disease: A culprit or a bystander?Ali Keshavarzian <sup>a</sup>, Phillip Engen <sup>a</sup>, Salvatore Bonvegna <sup>b</sup>, Roberto Cilia <sup>c</sup>  [Show more](#)  Share  Cite<https://doi.org/10.1016/bs.pbr.2020.01.004> [Get rights and content](#) 

---

Abstract

In recent years, large-scale metagenomics projects such as the Human Microbiome Project placed the gut microbiota under the spotlight of research on its role in health and in the pathogenesis several diseases, as it can be a target for novel therapeutical approaches. The emerging concept of a microbiota modulation of the gut-brain axis in the pathogenesis of neurodegenerative disorders has been explored in several studies in animal models, as well as in human subjects. Particularly, research on changes in the composition of gut microbiota as a potential trigger for alpha-synuclein ( $\alpha$ -syn) pathology in Parkinson's disease (PD) has gained increasing interest. In the present review, we first provide the basis to the understanding of the role of gut microbiota in healthy subjects and the molecular basis of the gut-brain interaction, focusing on metabolic and neuroinflammatory factors that could trigger the alpha-synuclein conformational changes and aggregation. Then, we critically explored preclinical and clinical studies reporting on the changes in gut microbiota in PD, as compared to healthy subjects. Furthermore, we examined the relationship between the gut microbiota and PD clinical features, discussing data consistently reported across studies, as well as the potential sources of inconsistencies. As a further step toward understanding the effects of gut microbiota on PD, we discussed the relationship between dysbiosis and response to dopamine replacement therapy, focusing on Levodopa metabolism. We conclude that further studies are needed to determine whether the gut microbiota changes observed so far in PD patients is the cause or, instead, it is merely a consequence of lifestyle changes associated with the disease. Regardless, studies so far strongly suggest that changes in microbiota appears to be impactful in pathogenesis of neuroinflammation. Thus, dysbiotic microbiota in PD could influence the disease course and response to medication, especially Levodopa. Future research will assess the impact of microbiota-directed therapeutic intervention in PD patients.

---

## Section snippets

### Introductions and definitions

What is the **“Gut Microbiota”**? The gut microbiota is a complex ecological community composed by about 100 trillions of microbes inhabiting the human intestine, which influences both normal physiology and disease susceptibilities through its metabolic activities and host interactions (Lozupone et al., 2012). On the other hand, the term **“Microbiome”** refers to the collection of genetic material (genome)—bacteria, virus, archaea, fungi, and protozoa represented in the gut microbiota (Lozupone et al., 2012).

### Gut microbiota in the pathogenesis of Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disease in the United States affecting up to 1% of individuals older than age 60 (Tysnes and Storstein, 2017). Unfortunately, the incidence of Parkinson's disease is increasing in recent years, with expectations to affect over 3 million Americans with PD by 2035 (GBD 2016 Neurology Collaborators, 2018; Tysnes and Storstein, 2017). Symptoms and signs of PD are in large part due to loss of dopaminergic neurons in the substantia nigra ...

### Twin studies

Several microbial taxa and functional modules in the gut microbiome have been shown to be heritable (Xie et al., 2016). There is a widespread concordance in the composition, Single Nucleotide Polymorphisms (SNPs), and functional capacity of the gut microbiome between twins (specifically an increased concordance among monozygotic twins over dizygotic twins), supporting the hypothesis of a substantial host genetic influence (Xie et al., 2016). Immune traits are also highly heritable and human...

### Environmental factors

Although genetics is involved in shaping our microbiota community (Gilbert et al., 2018), environmental factors have far more impact in determining the type of microbiota community we have in our GI tract (Gilbert et al., 2018; Hirschberg et al., 2019). For example, although the intestinal microbiota community is more similar between twins compared to unrelated subjects, the microbiota community is significantly different even between identical twins (Faith et al., 2013; Turnbaugh et al., 2009...

### Nasal and oral microbiota

The intestinal microbiota does not appear to be the only microbiota that is disrupted in PD patients. To date, there are two studies that interrogated the nasal and oral microbiota community structure and composition in PD patients. Pereira et al. interrogated both nasal and oral microbiota profiles (using oro-nasal wash sample) between PD patients and healthy controls (Pereira et al., 2017). The oral microbiota composition was significantly altered in PD patients, compared to healthy controls, ...

### Preclinical studies

Regardless of whether microbiota is the initial trigger or not, it could still be a major player in the pathogenesis of PD because bacterial associated pro-inflammatory factors may trigger or sustain neuroinflammation that is required for DA loss in PD. Several in vitro and rodent studies support this notion....

### Are gut microbiota changes a cause or a consequence of Parkinson's disease?

The causal link between dysbiotic microbiota and the development of PD is yet to be established. The debate is whether these changes in microbiota community structure and composition in PD is the trigger for PD, or are a consequence of PD. Indeed, several studies have shown a correlation between changes in microbiota and duration of the disease and dysbiosis is more pronounced in those with longer duration of PD (Hasegawa et al., 2015; Keshavarzian et al., 2015; Li et al., 2017; Minato et al.,...

### Interventions on gut microbiota as potential disease modifying strategies?

Taken as a whole, the data present in this book chapter supports the notion that gut microbiota-directed interventions could be the novel therapy that may not only improve symptoms and augment the effects of current therapy, but could also modify disease course and even prevent the onset of disease by reducing neuroinflammation.

Taken together, as discussed above, multiple cross-sectional clinical studies have now shown that PD patients exhibit a dysbiotic, “pro-inflammatory” microbiota and that ...

### Does PD start in the gut?

In the present chapter, we have described the evidences suggesting a potential causative role of gut dysbiosis (triggered by environmental factors in genetically susceptible host) in the pathogenesis of local (gut and CNS) and systemic inflammation and its relationship with microglia activation in animal models and in human subjects. According to the Braak's hypothesis, the initial site of aggregation of misfolded  $\alpha$ -syn may be either the gut or the olfactory bulb. Concerning the gut-to-brain...

### Conclusions

In this review, we propose that: (1) A disrupted microbiota gut-brain axis plays a critical role in the pathogenesis of PD and dysbiotic microbiota could be the trigger and/or enabler for neuro-inflammation that is required for neurodegeneration and DA loss in PD; (2) Dysbiotic microbiota could be the mechanism by which risk factors like environmental factors (stress, diet, disrupted circadian/sleep) and/or diseases (inflammatory bowel disease, metabolic syndrome/diabetes) promote PD and thus...

### Acknowledgments

A.K. and P.E. would like to thank Drs. Christopher B. Forsyth, Robin M. Voigt, Geethika Earthineni and Ms. Vivian Ramirez, and Shohreh Raeisi for their contribution to this book chapter. A.K. would also like to acknowledge philanthropy funding from Mrs. Barbara and Mr. Larry Field, Mrs. Ellen and Mr. Philip Glass,

and Mrs. Marcia and Mr. Silas Keehn. R.C. would like to thank Dr. Emanuele Cereda for brainstorming on the relationship between gut microbiota and PD pathophysiology as well as his...

---

## References (297)

J.K. Goodrich *et al.*

[Genetic determinants of the gut microbiome in UK twins](#)

Cell Host Microbe (2016)

A. Gonzales *et al.*

[Development of a specific ELISA to measure BACE1 levels in human tissues](#)

J. Neurosci. Methods (2011)

S. Ghaisas *et al.*

[Gut microbiome in health and disease: linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases](#)

Pharmacol. Ther. (2016)

A. Gerhard *et al.*

[In vivo imaging of microglial activation with \[11C\]\(R\)-PK11195 PET in idiopathic Parkinson's disease](#)

Neurobiol. Dis. (2006)

V. Ganapathy *et al.*

[Transporters and receptors for short-chain fatty acids as the molecular link between colonic bacteria and the host](#)

Curr. Opin. Pharmacol. (2013)

S. Fujioka *et al.*

[Occurrence of Crohn's disease with Parkinson's disease](#)

Parkinsonism Relat. Disord. (2017)

A. Fasano *et al.*

[Gastrointestinal dysfunction in Parkinson's disease](#)

Lancet Neurol. (2015)

N. Dzamko *et al.*

[Inflammation is genetically implicated in Parkinson's disease](#)

Neuroscience (2015)

H.B. Dodiya *et al.*

[Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease](#)

Neurobiol. Dis. (2020)

D. Devos *et al.*

## Colonic inflammation in Parkinson's disease

Neurobiol. Dis. (2013)



View more references

---

Cited by (53)

## Gut-brain axis through the lens of gut microbiota and their relationships with Alzheimer's disease pathology: Review and recommendations

2023, Mechanisms of Ageing and Development

Show abstract

## The bioaccessibility, bioavailability, bioactivity, and prebiotic effects of phenolic compounds from raw and solid-fermented mulberry leaves during in vitro digestion and colonic fermentation

2023, Food Research International

Show abstract

## Oral ingestion of the environmental toxicant trichloroethylene in rats induces alterations in the gut microbiome: Relevance to idiopathic Parkinson's disease

2022, Toxicology and Applied Pharmacology

Show abstract

## The gut-brain axis and sodium appetite: Can inflammation-related signaling influence the control of sodium intake?

2022, Appetite

### Citation Excerpt :

...The gut-brain axis can be defined as two-way biochemical signaling between the gastrointestinal tract and the central nervous system and, along with the resident gut microbiome composition and characteristics, has recently been implicated as a factor affecting a number of behaviors. The growing attention drawn to the gut-brain axis come, mostly, from the new findings indicating that qualitative and quantitative changes in the resident microbiome are related with chronic and non-transmissible diseases, like salt-related hypertension (Wilck et al., 2017), Alzheimer's (Szablewski, 2018), Parkinson's disease (Keshavarzian, Engen, Bonvegna, & Cilia, 2020) and some psychiatric diseases, and that quantitative changes in dietary composition can affect or modify the gut microbiome (Morais et al., 2021; Wilck et al., 2017). Early studies with germ-free mice established a connection between the gut microbiome with the host energy metabolism and obesity by showing that germ-free mice had decreased body fat despite having, interestingly, higher food intake (Backhed et al., 2004)...

Show abstract

## An open label, non-randomized study assessing a prebiotic fiber intervention in a small cohort of Parkinson's disease participants

2023, Nature Communications

## The overlooked benefits of hydrogen-producing bacteria

2023, Medical Gas Research



View all citing articles on Scopus

---

### Recommended articles (6)

Research article

#### Novel approaches to counter protein aggregation pathology in Parkinson's disease

Progress in Brain Research, Volume 252, 2020, pp. 451-492

[Show abstract](#) ✓

Research article

#### The Gut and Nonmotor Symptoms in Parkinson's Disease

International Review of Neurobiology, Volume 134, 2017, pp. 787-809

[Show abstract](#) ✓

Research article

#### The Link between Gut Dysbiosis and Neuroinflammation in Parkinson's Disease

Neuroscience, Volume 432, 2020, pp. 160-173

[Show abstract](#) ✓

Research article

#### Gut microbiota in Parkinson disease in a northern German cohort

Brain Research, Volume 1667, 2017, pp. 41-45

[Show abstract](#) ✓

Research article

#### The link between the gut microbiota and Parkinson's Disease: A systematic mechanism review with focus on $\alpha$ -synuclein transport

Brain Research, Volume 1769, 2021, Article 147609

[Show abstract](#) ✓

Research article

#### Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression

[Show abstract](#) ✓

---

[View full text](#)

Copyright © 2020 Elsevier B.V. All rights reserved.



Copyright © 2023 Elsevier B.V. or its licensors or contributors.  
ScienceDirect® is a registered trademark of Elsevier B.V.

