Proceedings of ICMMGH 2026 Symposium: Biomedical Imaging and AI Applications in Neurorehabilitation
DOI: 10.54254/2753-8818/2026.AU29633

Gut Microbiota – Overview of the Gut–Brain Axis and Its Association with Protein Misfolding in Parkinson's Disease

Junxi Chen

Faculty of Arts & Science, University of Toronto, Ontario, Canada
frankkk.chen@mail.utoronto.ca

Abstract. Parkinson's disease (PD) is a long-term neurodegenerative disorder best known for its motor symptoms, though many patients also experience non-motor issues. A key feature of PD is the abnormal folding and buildup of α-synuclein, which disrupts normal neuron function and contributes to the loss of dopaminergic cells. In recent years, researchers have started to look beyond the brain and found that the gut might play a major part in the disease process. The gut–brain axis, a communication system linking the nervous, immune, and metabolic systems, appears to connect gut health with PD pathology. The gut microbiota help maintain immune balance and barrier function, but when this balance is disturbed, inflammation and oxidative stress can promote α-synuclein aggregation. This review brings together recent evidence on how the gut microbiome, intestinal permeability, and inflammation may interact with α-synuclein misfolding. It also looks at possible therapeutic approaches, including diet, probiotics, and microbiota-based treatments, while pointing out the limits of current studies and the need for more causal research.

Keywords: Parkinson's disease, gut–brain axis, gut microbiota, α-synuclein aggregation, dysbiosis

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that mainly affects movement but also causes a variety of non-motor symptoms. It is marked by the gradual loss of dopaminergic neurons in the substantia nigra and by the accumulation of α-synuclein in Lewy bodies and Lewy neurites [1]. These abnormal protein aggregates interfere with normal neuron activity and lead to cell death. Interestingly, α-synuclein buildup isn't limited to the brain. It has also been found in the enteric nervous system (ENS), which suggests that some aspects of PD might start outside the brain [2].

The gut–brain axis describes a two-way communication network linking the gut and the central nervous system through neural, immune, hormonal, and metabolic pathways [3]. The gut microbiota play a central role in this system by producing metabolites, regulating immune function, and maintaining the intestinal barrier [4]. When this microbial balance is disturbed, or dysbiosis occurs, it can promote inflammation and other changes that may influence the nervous system.

Clinical and experimental data support this idea. Many PD patients experience constipation and other gastrointestinal issues long before they develop movement problems [5]. Animal models show

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.AU29633

that gut microbes can affect α-synuclein aggregation and neuroinflammation [6]. Epidemiological studies also suggest that cutting the vagus nerve—a procedure known as truncal vagotomy—lowers PD risk, which supports the gut-to-brain connection [7].

In this review, I discuss how gut microbes and the gut–brain axis might contribute to α-synuclein misfolding and PD development. The paper first reviews α-synuclein's structure and role in neurons, then explores how microbial imbalance and inflammation could drive PD pathology, and finally considers possible therapeutic strategies that target the microbiota.

2. α-Synuclein misfolding and pathology

2.1. Physiological role of α-Synuclein

α-Synuclein is a small protein made up of 140 amino acids that is found in high amounts in neurons, especially at presynaptic terminals. It has three main parts: the N-terminal region that helps it bind to membranes, a middle section known as the non-amyloid-β component (NAC) region that promotes aggregation, and a negatively charged C-terminal region that keeps the protein soluble. Under normal conditions, α-synuclein doesn't have a fixed shape but can fold into α-helices when it binds to synaptic vesicles [8].

In healthy neurons, α-synuclein helps with vesicle trafficking and neurotransmitter release by supporting SNARE complex formation [8]. This function is particularly important in dopaminergic neurons, where the protein helps regulate dopamine storage and release. Studies using α-synuclein knockout mice show that its absence leads to altered dopamine signaling and reduced synaptic plasticity.

Genetic studies highlight its relevance to PD. Duplications or triplications of the SNCA gene cause familial PD, while specific mutations like A53T and E46K increase α-synuclein aggregation and lead to early-onset disease [9]. These findings show that α-synuclein plays an essential role in both normal neuronal activity and PD pathogenesis.

2.2. Oligomerization of α-Synuclein and aggregation

When α-synuclein misfolds into β-sheet structures, it forms small clumps called oligomers, which are particularly toxic [10]. These oligomers can damage membranes, disturb calcium signaling, and generate oxidative stress [11]. Over time, they grow into fibrils that cluster into Lewy bodies and neurites, the hallmark lesions of PD [12]. Misfolded α-synuclein also disrupts normal protein recycling by blocking autophagy and the ubiquitin–proteasome system [12]. Once fibrils form, they can recruit soluble α-synuclein and spread aggregation in a self-perpetuating cycle. Post-translational modifications, such as phosphorylation at serine-129 and nitration, further enhance aggregation and toxicity [13].

2.3. Braak's hypothesis on PD pathology

Braak and his colleagues proposed a staging model suggesting that PD pathology may begin in peripheral tissues, such as the enteric nervous system (ENS) or the olfactory bulb, and then spread toward the brain in a prion-like fashion through the vagus nerve. Over time, the pathology reaches deeper brain regions like the substantia nigra and neocortex [14]. This idea is supported by early clinical signs — for example, symptoms such as constipation and loss of smell often appear years before motor symptoms develop [15]. Autopsy studies have also found α-synuclein aggregates in the ENS of PD patients, even at very early stages of the disease [2].

DOI: 10.54254/2753-8818/2026.AU29633

Experimental work backs up this "gut-to-brain" route: when α-synuclein fibrils are injected into the intestinal wall of rodents, they can travel up the vagus nerve to reach brainstem regions [16]. However, not all cases follow this same pathway. Some patients seem to develop α-synuclein pathology primarily in the brain, without peripheral involvement, leading researchers to describe two possible subtypes of PD — "body-first" and "brain-first" [17].

3. Gut–brain axis in PD

3.1. Metabolic pathway (SCFAs, LPS, etc.)

Gut microbes produce a variety of metabolites that affect the brain, with short-chain fatty acids (SCFAs) being among the most important. SCFAs like acetate, propionate, and butyrate are made when bacteria ferment dietary fiber. They help regulate gene expression, immune function, and gut barrier strength [18]. For example, butyrate acts as a histone deacetylase inhibitor, giving it anti-inflammatory and neuroprotective properties. In germ-free mice, the absence of SCFAs causes microglia to stay in an immature state and weakens their immune response, but adding SCFAs back can fix these defects [18].

In PD, many studies have found a drop in SCFA-producing bacteria such as Faecalibacterium and Roseburia, along with lower levels of SCFAs in stool samples [19]. This decrease is linked to inflammation and impaired gut barrier function. PD patients often show higher levels of intestinal permeability markers, including zonulin and α1-antitrypsin, which point to a weakened intestinal lining [20]. When this barrier becomes "leaky," bacterial products like lipopolysaccharide (LPS) can enter the bloodstream and trigger immune responses.

LPS is a strong activator of inflammation. It binds to Toll-like receptor 4 (TLR4) on immune cells and starts a cascade through NF-κB that leads to the release of cytokines such as TNF-α and IL-1β. Long-term exposure to LPS can promote α-synuclein misfolding and cause inflammation in the brain [21]. In animal models, giving LPS peripherally increases α-synuclein aggregation and dopaminergic neuron loss, and PD patients have higher plasma levels of LPS-binding protein, which indicates ongoing exposure to bacterial endotoxins [20]. Altogether, these findings show that reduced SCFAs and increased pro-inflammatory products create an environment that supports PD development.

3.2. Neural pathway (vagus nerve, BBB, immune signals)

The vagus nerve is one of the main communication routes between the gut and the brain. Research in rodents shows that misfolded α-synuclein injected into the intestinal wall can move up the vagus nerve to the dorsal motor nucleus in the brainstem. When the vagus nerve is cut, this spread is blocked, showing that the nerve acts as a physical pathway for transmission [16].

Human studies support this connection too. Large population-based studies have found that people who had a truncal vagotomy had a lower chance of developing PD, although the protective effect seems to depend on how long the patients were followed and what kind of surgery was done [7]. Together, these findings support the idea that the vagus nerve may serve as a route for α-synuclein to move from the gut to the brain.

Inflammation that starts in the gut can also influence the brain indirectly by affecting the blood–brain barrier (BBB). Cytokines such as TNF-α and IL-6 can weaken tight junctions between endothelial cells, making the BBB more permeable and allowing immune cells and microbial molecules to enter the central nervous system [22]. In PD patients, pro-inflammatory T cells and

DOI: 10.54254/2753-8818/2026.AU29633

monocytes have been found in brain tissue and cerebrospinal fluid [23]. This suggests that gut-derived immune activation can extend beyond the intestines and contribute to brain inflammation and neuron loss.

3.3. Animal models and implications on humans

Animal studies provide strong evidence that the gut–brain axis plays a major role in Parkinson's disease. In germ-free α-synuclein transgenic mice, both motor problems and α-synuclein aggregation are reduced compared to mice with normal gut microbiota [6]. Interestingly, when these germ-free mice are colonized with microbiota from PD patients, their symptoms and aggregation worsen, while colonization with microbiota from healthy individuals does not produce the same effect [6].

Other models highlight more specific mechanisms. For example, when mice are colonized with E. coli that produce curli, a bacterial amyloid protein, α-synuclein aggregation increases. But when they are colonized with E. coli that lack curli, this effect doesn't occur [24]. Similarly, giving rodents peripheral injections of LPS increases α-synuclein buildup in the substantia nigra [20].

Findings in humans are consistent with these animal studies. Imaging has shown altered vagal nerve activity in PD patients, and biological markers point to increased gut permeability and systemic inflammation [19, 25]. Together, animal and human evidence supports the gut–brain axis as an active player in PD pathogenesis rather than just a secondary effect.

4. Gut microbiota in PD

4.1. Changes in microbial composition and functional implication

Studies across Europe, North America, and Asia have found distinct gut microbiome changes in PD. Butyrate-producing bacteria such as Faecalibacterium, Roseburia, and Blautia are consistently reduced, while mucin-degrading and pro-inflammatory species like Akkermansia and Enterobacteriaceae are increased [26, 27]. These changes likely reduce SCFA availability, weaken the gut barrier, and promote inflammation.

Functional studies of the gut microbiome in PD show an increase in bacterial genes involved in lipopolysaccharide (LPS) production and a decrease in those associated with butyrate synthesis [28]. This change suggests that the microbial environment shifts toward a more inflammatory state.

Long-term studies show that people with REM sleep behavior disorder (RBD), a condition that often develops before PD, show lower levels of SCFA-producing bacteria years before any motor symptoms appear [15]. This finding implies that changes in the gut microbiota might start early, possibly long before PD is diagnosed.

4.2. Microbial metabolites and their role in PD

Microbial metabolites are now recognized as major messengers in gut–brain communication. Beyond SCFAs, bacterial amyloids such as curli fibers, made by Escherichia coli and similar species, can influence PD by mimicking human amyloids. These curli fibers can directly trigger α-synuclein aggregation both in vitro and in vivo [24]. In rodents, exposure to curli-producing bacteria worsens α-synuclein pathology and motor symptoms, showing that bacterial amyloids can act as disease-promoting agents.

A lack of SCFAs further makes this problem worse. These fatty acids are crucial for keeping the gut barrier intact and for supporting healthy microglial function in the brain [20]. When they are

DOI: 10.54254/2753-8818/2026.AU29633

reduced, the gut becomes more permeable to harmful substances such as LPS, and microglia become hyperactive, leading to inflammation in the brain. These effects together create a feedback loop that drives both α-synuclein aggregation and neuroinflammation.

Overall, these results provides another link between gut dysbiosis, α-synuclein misfolding, and the gradual progression of PD.

5. Microbiota-induced α-Synuclein aggregation

5.1. Proposed mechanisms from studies (cross-seeding, toxins, stress)

One of the most direct ways the gut microbiota can influence PD is through cross-seeding of α-synuclein by bacterial amyloids. Curli fibers, which are produced by Escherichia coli and other Enterobacteriaceae, share structural features with human amyloids. In vitro experiments have shown that curli can promote α-synuclein fibril formation, while in vivo studies demonstrate that exposure to curli-producing bacteria increases α-synuclein aggregation and speeds up motor decline in rodent models [24].

Besides amyloids, other bacterial products such as toxins and inflammatory molecules can also promote α-synuclein misfolding. Lipopolysaccharide (LPS) is a well-known example. When LPS binds to TLR4, it activates inflammatory signaling pathways that release cytokines, which can damage neurons and increase α-synuclein production in enteric neurons [21]. In addition, long-term oxidative stress caused by microbial metabolites or environmental toxins can make protein folding less stable, further promoting aggregation [29]. Together, these factors create a gut environment that strongly favors α-synuclein misfolding and aggregation.

5.2. Animal model evidence (germ-free vs colonized mice)

Animal studies provide strong evidence that gut microbes can directly influence α-synuclein aggregation. In germ-free α-synuclein transgenic mice, both motor symptoms and α-synuclein buildup are reduced compared to mice with normal gut microbiota [6]. When these germ-free mice are colonized with microbiota from PD patients, their pathology worsens, while colonization with microbiota from healthy donors does not produce the same effect [6]. In addition, mice colonized with curli-producing E. coli show greater α-synuclein aggregation and more severe motor problems, whereas colonization with E. coli strains lacking curli has no such effect [25].

5.3. Role of peripheral inflammation and intestinal homeostasis disruption

A disrupted gut barrier acts as a gateway between dysbiotic microbes and the body. PD patients often have higher levels of permeability markers such as zonulin and α1-antitrypsin, consistent with a “leaky gut” [20]. This allows bacterial components like LPS and amyloids to enter circulation and trigger immune responses. Inflammatory cytokines such as TNF-α and IL-6 not only upregulate α-synuclein production in enteric neurons but can also cross the BBB and activate microglia [30]. These interactions create a self-reinforcing cycle linking inflammation, α-synuclein aggregation, and neurodegeneration.

DOI: 10.54254/2753-8818/2026.AU29633

6. Therapeutic and clinical implications

6.1. Probiotics and prebiotics

Because gut dysbiosis plays a role in PD, researchers have tested probiotics and prebiotics as potential treatments. A randomized controlled trial found that multi-strain probiotics improved bowel motility and reduced some non-motor symptoms [31]. Another study using Hexbio probiotics also reported relief from constipation and better gut motility [32]. Similarly, inulin-based prebiotics raised SCFA levels and reduced gut inflammation in PD patients [33]. These findings suggest that restoring a healthy microbiota could help manage PD symptoms and possibly slow progression

6.2. Fecal Microbiota Transplantation (FMT)

FMT, which transfers gut microbes from healthy donors to patients, has shown mixed outcomes. A randomized trial found significant microbial changes after FMT but no clear improvement in motor symptoms [34]. However, smaller phase-2 studies did report modest improvements in both motor and non-motor measures [35]. Differences in donors, patient characteristics, and methods may explain the inconsistent results, indicating that FMT still needs refinement before it can be widely used.

6.3. Dietary interventions

Diet offers a simple and sustainable way to support gut health. The Mediterranean diet—rich in fiber, healthy fats, and polyphenols—has been linked to higher microbial diversity and better cognitive and motor outcomes in PD patients [36]. More recent studies also show that following this diet improves constipation and reduces gut inflammation [37].

6.4. Drug–microbiota interactions

Gut bacteria can also influence how PD medications work. Enterococcus faecalis converts levodopa to dopamine in the gut, reducing how much of the drug reaches the brain, while Enterococcus lenta further metabolizes dopamine [38]. Blocking bacterial enzymes that carry out these reactions restores levodopa levels in preclinical studies. This shows that the gut microbiota not only affect disease mechanisms but can also alter drug effectiveness, which is an important factor in PD management.

7. Conclusion

Parkinson's disease is now recognized as a condition that affects many systems, not just the brain, with α-synuclein misfolding sitting at the center of it all. Evidence from both animal and human studies supports the gut–brain axis as an important part of this process. Gut dysbiosis, a weakened intestinal barrier, and chronic immune activation all seem to work together to promote α-synuclein buildup and neuronal damage.

Even though these links are well established, a lot of questions are still open. Most human studies are cross-sectional, which makes it hard to tell whether gut changes cause the disease or simply appear as a result of it. Differences in where samples are taken from, the sequencing methods used, and how the data are analyzed also lead to mixed findings. On top of that, lifestyle factors such as diet, regional differences, and medication use further complicate interpretation. To move forward,

DOI: 10.54254/2753-8818/2026.AU29633

the field will need standardized approaches and long-term studies that can help distinguish cause from consequence.

Looking to the future, the gut microbiome could become a powerful tool for early PD detection, especially if reliable microbial biomarkers are developed for the prodromal stage, when treatment might make the biggest difference. Tailored therapies—like personalized probiotic or prebiotic regimens, or dietary adjustments—may also become part of future care. Ultimately, a full understanding of how gut microbes contribute to PD will require collaboration across neuroscience, microbiology, immunology, and computational biology, bringing these disciplines together to turn biological insight into real treatments.

References

[1] Spillantini MG, et al. α-Synuclein in Lewy bodies. Nature. 1997; 388: 839–40.
[2] Shannon KM, et al. Colonic α-synuclein pathology in early PD. PLoS One. 2012; 7: e36600.
[3] Cryan JF, et al. The microbiota–gut–brain axis. Physiol Rev. 2019; 99: 1877–2013.
[4] Wallen ZD, et al. Dysbiosis of the gut microbiome in PD. NPJ Parkinson's Dis. 2020; 6: 16.
[5] Roos DS, et al. Prodromal non-motor symptoms of PD. NPJ Parkinson's Dis. 2022; 8: 14.
[6] Sampson TR, et al. Gut microbiota regulate α-syn pathology. Cell. 2016; 167: 1469–80.
[7] Svensson E, et al. Vagotomy and PD risk. Ann Neurol. 2015; 78: 522–9.
[8] Burré J. Synaptic function of α-synuclein. Neuron. 2015; 87: 10–2.
[9] Singleton AB, et al. SNCA triplication causes PD. Science. 2003; 302: 841.
[10] Lashuel HA, et al. Toxic α-syn oligomers. J Neurochem. 2013; 129: 746–57.
[11] Devi L, et al. α-Syn inhibits mitochondrial complex I. J Biol Chem. 2008; 283: 9089–9100
[12] Cuervo AM, et al. Mutant α-syn impairs CMA. Science. 2004; 305: 1292–5.
[13] Oueslati A. PTMs of α-synuclein in PD. Mol Neurodegener. 2016; 11: 79.
[14] Braak H, et al. Staging of PD pathology. Neurobiol Aging. 2003; 24: 197–211.
[15] Heinzel S, et al. Prodromal PD & RBD criteria. Lancet Neurol. 2021; 20: 283–92.
[16] Kim S, et al. Gut-to-brain α-syn propagation via vagus. Neuron. 2019; 102: 627–43.
[17] Borghammer P, Van Den Berge N. Brain-first vs body-first PD. J Parkinsons Dis. 2019; 9(S2): S281–95.
[18] Erny D, et al. SCFAs control microglia. Nat Neurosci. 2015; 18: 965–77.
[19] Scheperjans F, et al. Gut microbiota differences in PD. Mov Disord. 2015; 30: 135–44.
[20] Forsyth CB, et al. Gut permeability in PD. PLoS One. 2011; 6: e28032.
[21] Qin L, et al. Systemic LPS causes chronic neuroinflammation. J Neurochem. 2007; 100: 136–45.
[22] Banks WA. BBB in neuroimmunology. Brain Behav Immun. 2016; 57: 1–10.
[23] Hirsch EC, Standaert DG. Neuroinflammation in PD. Nat Rev Neurol. 2021; 17: 159–75.
[24] Sampson TR, et al. Curli-producing bacteria promote α-syn aggregation. eLife. 2020; 9: e53111.
[25] Wang H, et al. Altered vagal activity in PD (fMRI). Auton Neurosci. 2019; 220: 102548.
[26] Heintz-Buschart A, et al. Nasal/gut microbiome in PD. Mov Disord. 2018; 33: 657–66.
[27] 37Bedarf JR, et al. Microbiota functional implications in early PD. Mov Disord. 2017; 32: 739–49.
[28] Romano S, et al. Meta-analysis of gut microbiome in PD. NPJ Parkinson's Dis. 2021; 7: 17.
[29] Zow W, et al. Oxidative stress destabilizes α-synuclein in PD. Mol Neurodegener. 2016; 11: 79.
[30] Kelly LP, et al. Peripheral inflammation & ENS α-syn. Acta Neuropathol Commun. 2014; 2: 31.
[31] Tan AH, et al. Probiotics for constipation in PD: RCT. Neurology. 2021; 96: e772–82.
[32] Ibrahim A, et al. Hexbio probiotics improve constipation in PD. PLOS ONE. 2020; 15: e0244680.
[33] Hall DA, et al. Prebiotic inulin increases SCFAs in PD. Front Neurol. 2023; 14: 1135678.
[34] Scheperjans F, et al. FMT for PD: RCT. JAMA Neurol. 2024; 81: 925–38.
[35] Bruggeman A, et al. Phase-2 FMT trial (GUT-PARFECT). eClinicalMedicine. 2024; 71: 102563.
[36] Titova N, et al. Mediterranean diet & PD. Mov Disord. 2018; 33: 416–24.
[37] Rusch C, et al. Mediterranean diet improves constipation in PD: RCT. Nutrients. 2024; 16: 1134.
[38] Maini Rekdal V, et al. Gut bacteria metabolize levodopa. Science. 2019; 364: eaau6323.