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REVIEW

# A Brief Overview of Gut-Associated α-Synuclein Pathology

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**ABSTRACT:** Lewy body diseases (LBD), including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), are neurodegenerative disorders characterized by the intracellular aggregation and accumulation of α-Synuclein (αSyn), leading to neuronal death. Although these diseases primarily present with symptoms affecting the central nervous system (CNS), such as motor and cognitive impairment, increasing research suggests that their roots may be found in the gut. This review summarizes recent findings and key historical insights into the involvement of the gut in αSyn pathology. The topics covered include pathological observations in patients with LBD, animal models investigating the propagation of αSyn from the gut to the brain, intestinal inflammation, alterations in the gut microbiome, and the molecular mechanisms of αSyn pathology within enteric neurons. These topics are essential for understanding the involvement of the gut in αSyn pathology and provide foundational insights that may lead to future therapeutic applications.

**KEYWORDS:** α-Synuclein; Lewy body disease; Parkinson's disease; dementia with Lewy bodies; enteric nervous system; gut-brain axis

## 1 Introduction

Currently, there are no fundamental cures for diseases linked to the α-Synuclein (αSyn) protein, such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). These diseases are collectively referred to as Lewy body diseases (LBD) due to pathological hallmarks observed in the brain, such as Lewy bodies and Lewy neurites, which are mainly composed of αSyn [1]. The aggregation and accumulation of αSyn leads to neuronal cell death, resulting in motor and cognitive impairment [2]. In addition to these symptoms, non-motor symptoms, such as gastrointestinal dysfunction and sleep disorders, often precede motor and cognitive impairments [3]. The hypothesis proposed by Braak et al. that αSyn spreads from the enteric nervous system (ENS) to the brain via the vagus nerve as part of the progression of idiopathic PD is consistent with the pathophysiology in which gastrointestinal symptoms and autonomic dysfunction precede motor and cognitive impairments [4–6]. In recent years, this hypothesis has been validated using animal experiments [7,8]. Truncal vagotomy has been suggested to reduce the risk of developing PD [9,10]. Although this hypothesis may not apply to all patients with PD, it is recognized as a plausible explanation for the onset and progression of the disease [11].

If LBD originates in the gut, it may be possible to prevent or treat it by targeting the gut in the future. To achieve this, the detailed mechanisms by which αSyn induces gut pathology must be elucidated.

Unfortunately, research on αSyn pathology has primarily focused on the central nervous system, leaving many aspects of gut pathology unclear.

This review aims to provide an overview of studies that may lead to the elucidation of the pathological mechanisms of αSyn in the gut (Fig. 1). The first half introduces the fundamental relationship between LBD and the gut, as well as animal models used to demonstrate the propagation of αSyn pathology from the gut to the brain. The second half highlights studies that contribute to the understanding of the detailed pathological mechanisms in the gut, which are crucial for identifying future therapeutic targets. Specifically, it discusses research on the relationship between intestinal inflammation, gut microbiota, and αSyn pathology, as well as the dynamics of αSyn in the enteric neurons.

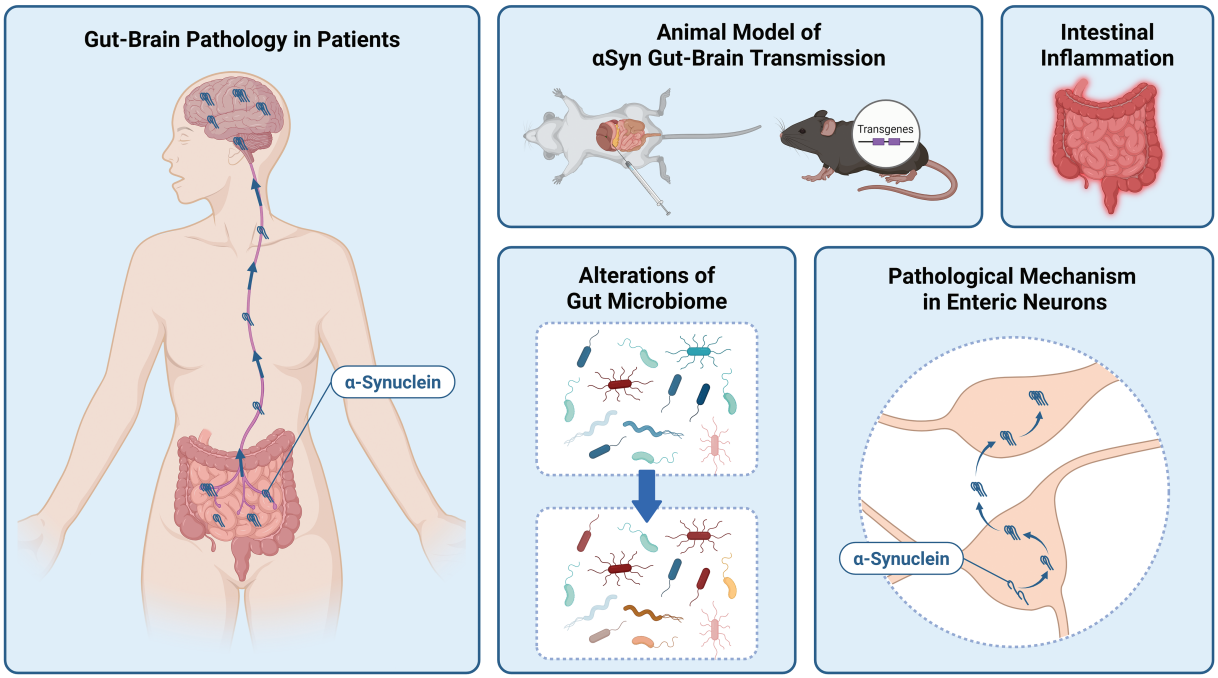


**Figure 1:** Topics of this review. Created in BioRender. Sekimori, T. (2025) https://BioRender.com/4n42m39 (accessed on 14 September 2025)

## 2 Gastrointestinal Pathology in Patients with Lewy Body Disease

This section discusses the relationship between LBD and gastrointestinal pathology in patients, as revealed by clinical symptoms and pathological analyses. Gastrointestinal dysfunction is one of the most common non-motor symptoms observed in patients with PD [12]. Constipation is the most prevalent symptom, with a reported prevalence ranging from 20% to 80% in patients with PD [12–18]. A prospective study conducted prior to the onset of PD showed that men with fewer than one bowel movement per day had a higher risk of developing PD than those with at least one bowel movement per day [19]. Constipation is considered an early clinical symptom of PD and is believed to precede motor symptoms by more than ten years [3,13,20,21].

Braak and colleagues, who proposed pathological staging of sporadic PD, identified the dorsal motor nucleus of the vagus nerve (DMV) as one of the earliest sites of central nervous system (CNS) involvement in PD [4–6]. This finding suggests the possibility of αSyn pathology propagating from the gut to the brain. The unmyelinated preganglionic fibers originating from the DMV make direct contact with ganglion cells in Auerbach's (myenteric) plexus of the gut, indicating that the ENS and CNS are anatomically connected

via the vagus nerve [6]. Indeed, Histopathological studies conducted in the 1980s reported the presence of Lewy bodies in the enteric nervous system of patients with PD [22–24]. Recent research has demonstrated αSyn immunoreactivity in duodenal biopsies obtained from early stage, untreated patients with PD with a disease duration of less than four years [25]. In the next section, we introduce a study that verified whether αSyn pathology spreads through the communication pathway between the ENS and CNS.

## 3 Animal Model for Verifying Gut-Brain Transmission of α-Synuclein

Studies using several animal models have demonstrated the spread of αSyn pathology from the intestine to the brain. This section introduces these studies, which are divided into injection and transgenic models. As described below, multiple animal model experiments suggest that αSyn propagates from the gut to the brain via the vagus nerve.

### *3.1 Injection Models*

One of the most representative models for studying this transmission is the injection of αSyn into the gastrointestinal walls of mice or rats. Prior to the development of this model, a study showed that injecting brain extracts from patients with DLB into the gastric wall of A53T αSyn transgenic rats led to the time-dependent formation of αSyn aggregates in enteric neurons up to four months post-injection [26]. In another study, brain extracts from patients with PD were injected into the gastric wall of wild-type rats [27]. Within 48 h, clear αSyn immunoreactivity was observed in vagal nerve fibers, and by 72–144 h, αSyn was transported to the DMV. Furthermore, recombinant αSyn in different conformations (monomers, oligomers, and fibrils) was also shown to be transported to the DMV when injected into the gastrointestinal wall. Kim et al. conducted an experiment in which αSyn preformed fibrils (PFFs) were injected into the muscular layer of the pylorus and duodenum in mice [7]. By seven months post-injection, immunoreactivity for phosphorylated αSyn on serine 129 (pSer129-αSyn) had spread from the gut to various brain regions, including the DMV, substantia nigra pars compacta, hippocampus, striatum, and prefrontal cortex. Notably, this propagation was abolished by vagotomy, indicating the critical role of the vagus nerve in the transmission. In other words, studies using these injection models demonstrate that α-Synuclein propagates from the gut to the brain in a prion-like manner via the vagus nerve. Additional studies using similar models have been conducted [28–33]. The experimental conditions and findings of these studies were well summarized in a review by Polinski [8].

### *3.2 Transgenic Mouse Models*

Several limitations have been identified in the abovementioned injection models. One major concern is that the levels of injected αSyn are extremely high, which may result in observed toxicity that does not accurately reflect the actual pathophysiological conditions [34]. Additionally, variability in experimental outcomes has been attributed to differences in the properties of αSyn PFFs, their dosage, and injection sites [35]. To address these issues, a novel transgenic mouse model was recently developed [35]. This model utilizes a tetracycline-inducible system to express either the αSyn N103 fragment, Tau N368 fragment, or both in the ENS. Human αSyn is cleaved at N103 by asparagine endopeptidase (AEP), and this fragmentation influences its pathological activity [36]. In transgenic mice expressing αSyn N103 or both αSyn N103 and Tau N368 in the ENS, time-dependent aggregation of αSyn was observed in the brain, with particularly prominent aggregates in mice expressing both fragments [35]. Moreover, vagotomy in mice expressing both αSyn N103 and Tau N368 resulted in reduced αSyn aggregation in the brain.

Additionally, studies have investigated the spread of αSyn from intestinal epithelial cells to the vagus nerve. It has been shown that enteroendocrine cells (EECs) in the intestinal mucosa directly connect with

neurons and express αSyn [37,38]. A transgenic mouse model expressing three forms of human αSyn (wild-type, A30P, and A53T mutants) exclusively in intestinal epithelial cells demonstrated αSyn seeding activity in the vagal ganglia. This suggests that pathological αSyn seeds may migrate from intestinal epithelial cells to the vagus nerve, which does not originally express pathological αSyn [39].

## 4 Intestinal Inflammation and α-Synuclein Pathology

Studies using animal models of LBD have suggested a link between gastrointestinal dysfunction, αSyn accumulation in the gut, and intestinal inflammation. In this section, we introduce research focusing on enteric glial cells, key players in inflammation, and Toll-like receptor 2 (TLR2), a molecule involved in subsequent inflammatory responses.

### *4.1 Modulation of Enteric Glial Cells*

Enteric glial cells (EGCs) are classified into four distinct morphological types: protoplasmic, fibrous, mucosal, and intramuscular [40]. *Sox10*, *S100b*, and *Plp1* are expressed in all classes of enteric glial cells, whereas *Gfap* is specifically expressed in glial cells of the myenteric plexus [41]. Moreover, *Gfap* expression varies depending on cellular and tissue conditions and may serve as a valuable marker under inflammatory conditions [41]. Studies using various animal models of PD have suggested the involvement of EGCs in PD. In a chronic MPTP/probenecid-treated mouse model, αSyn oligomers were found to colocalize with glial fibrillary acidic protein (GFAP)-positive EGCs in the myenteric plexus [42]. Furthermore, following acute MPTP administration, increased levels of 4-hydroxynonenal (4-HNE), a marker of oxidative stress-induced cellular damage, and nitrated αSyn were observed in the stomach EGCs.

Transgenic (Tg) mice expressing human αSyn with the A53T mutation develop motor impairments between 9–16 months of age [43]. Prior to this, by 3 months of age, they exhibit gastrointestinal dysfunction and αSyn aggregates in the enteric neurons of the muscular and submucosal layers of the colon [44]. In both Tg and wild-type mice, an age-dependent decrease in Sox10- and S100β-positive EGCs was observed, with Tg mice showing earlier reductions at 12 weeks compared to wild type mice [45]. Another study using A53T Tg mice reported an increase in GFAP-positive glial cells [46]. In a rotenone-induced PD rat model, decreased immunoreactivity for S100β and GFAP in the gut was reported, along with increased immunoreactivity for ionized calcium-binding adapter molecule 1 (IBA-1), a marker for microglia and macrophages [47]. While some studies have reported a reduction in S100β-positive glial cells, other studies have shown an increase in these cells within the myenteric plexus of rats overexpressing αSyn following bilateral nigral injection of adeno-associated virus (AAV)-αSyn [48].

These findings suggest that the induction of αSyn pathology through various approaches affects EGCs expression. However, the nature of these changes varies depending on the model, and a unified understanding has not yet been reached.

### *4.2 Expression Dynamics of Toll-Like Receptor 2*

In connection with the involvement of enteric EGCs, changes in Toll-like receptor 2 (TLR2), which plays a role in the progression of inflammation, have been observed in animal studies. TLR2 is a receptor that recognizes a variety of products from both gram-negative and gram-positive bacteria, including lipoteichoic acid, lipoproteins, peptidoglycans, and bacterial amyloids, as well as endogenous factors such as αSyn [49]. In the gut, TLR2 expression has been reported in neurons, glial cells, and smooth muscle cells [50].

A study investigating the inflammatory state in A53T Tg mice found increased levels of interleukin (IL)-1β and tumor necrosis factor (TNF) in the colon and activation of enteric glial cells from 3 months of

age [46]. Caspase-1 activity in the colon was significantly elevated at both 3 and 9 months, suggesting that early stage αSyn accumulation in the gut may lead to epithelial barrier disruption via activation of the classical caspase-1-dependent inflammasome signaling pathway. Additionally, an examination of toll-like receptor (TLR) 2 expression in the colon showed a reduction at 3 months, an increase at 6 months, and a return to non-Tg levels by 9 months in Tg mice. Plasma lipopolysaccharide (LPS) levels were significantly higher in Tg mice than in non-Tg mice at 3 months but were similar at 6 and 9 months.

In another model, the MPTP-induced mouse model, increased phosphorylated αSyn (p-αSyn) and gastrointestinal dysfunction were observed in the colon, along with elevated TLR2 expression [51]. p-αSyn and TLR2 were particularly co-localized in Schwann cells. Inhibition of TLR2 with CU-CPT22 (TLR1/TLR2 inhibitor) led to the recovery of fecal water content and suppression of inflammation, p-αSyn deposition, and Schwann cell activation. Schwann cells are the major glial cells of the peripheral nervous system [52]. In addition to supporting and protecting neurons, they can also be activated as immune competent cells and release cytokines and chemokines [52,53]. Based on this, it is conceivable that Schwann cell dysfunction may lead to neuronal damage either directly or indirectly through inflammatory responses.

TLR2 was a common factor in both studies. Although the expression patterns vary depending on the timing of observation and the model used, TLR2 may be an important player in gut inflammation associated with LBD. The expression of TLR2 highlights the complex link between gut microbiota and intestinal inflammation in relation to αSyn pathology, emphasizing the modulation of inflammatory pathways. Therefore, the next section focuses on the gut microbiome.

## 5 Gut Microbiota and α-Synuclein Pathology

The gut microbiota is an indispensable player in shaping the intestinal environment. In this section, we discuss the relationship between the gut microbiota and αSyn pathology.

Thy1-αSyn transgenic mice, which overexpress αSyn, exhibit progressive motor deficits and impaired colonic motility [54,55]. In these mice, motor dysfunction and αSyn aggregation in the substantia nigra, observed under antibiotic-treated specific pathogen-free (SPF) conditions, were suppressed under germ-free (GF) conditions, suggesting that gut microbes promote αSyn-induced motor deficits and brain pathology [56]. In patients with PD and DLB, an increase in the mucin layer-degrading *Akkermansia* and a decrease in short-chain fatty acid (SCFA)-producing bacteria have been observed [57,58].

Several species within the genus *Akkermansia* have been identified [59], beginning with *Akkermansia muciniphila* (*A. muciniphila*), which was first discovered in human feces by Derrien et al. in 2004 [60]. *A. muciniphila* is a mucin-degrading bacterium that can erode the intestinal mucus barrier under conditions of dietary fiber deficiency [61]. It has also been implicated in sulfur metabolism, particularly in the production of hydrogen sulfide [62]. These effects, enhanced intestinal permeability and metabolic alterations, are thought to be associated with the increased abundance of *A. muciniphila* in patients with Lewy body disease [59,63,64].

Short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, are produced by the fermentation of dietary fiber by gut microbiota [65]. Similar to the reduction in SCFA-producing bacteria observed in patients, a decrease in fecal levels of butyrate and propionate has also been reported from 3 months of age in human A53T αSyn transgenic mice, as described in the section on intestinal inflammation [46,57,58]. SCFAs possess neuroprotective properties, and oral administration of butyrate has been shown to improve motor impairment in MPTP-induced PD mice [66]. SCFAs exert neuroprotective effects through various mechanisms, including the regulation of microglial activation, reduction of oxidative stress, and enhancement of intestinal mucosal barrier integrity [67,68]. On the other hand, recent studies have reported that SCFAs

can promote αSyn pathology by activating NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasome via protein–coupled receptor (GPR) 43 signaling [69]. Further research is needed to clarify whether SCFAs suppress or promote αSyn pathology and under which conditions these effects occur. Although clinical trials targeting the restoration of SCFA levels in patients with Parkinson's disease remain scarce, prebiotic interventions have been shown to increase SCFA production [70,71].

## 6 Pathological Mechanisms of α-Synuclein in Enteric Neurons

If the initial lesions of LBD originate in the gut, it is essential to elucidate the detailed pathological mechanisms to develop treatments for prevention or cure of the disease. This section summarizes studies that investigated the pathological mechanisms of αSyn in enteric neurons using cultured cells and other models.

### *6.1 Expression of Endogenous α-Synuclein*

A study using primary cultured rat enteric neurons showed that membrane depolarization induced by potassium chloride (KCl) or increased intracellular cyclic adenosine monophosphate (cAMP) levels induced by forskolin treatment significantly elevated αSyn levels [72]. These treatments activate the Ras/extracellular signal-regulated kinase (ERK) pathway and induce αSyn expression. *In vivo* experiments in this study also confirmed increased αSyn expression in proximal colonic enteric neurons following depolarization or forskolin treatment.

Conversely, when primary cultured rat ENS cells were exposed to LPS or a combination of TNF-α and IL-1β, a decrease in αSyn expression was observed, which was linked to the p38 signaling pathway [73]. Similar experiments using primary cultured rat cortical neurons or erythroid leukemia cells did not show any changes in αSyn expression. Additionally, reduced αSyn expression was observed in a mouse model of acute colitis induced by dextran sulfate sodium (DSS), further supporting the involvement of inflammatory cytokines, such as TNF-α and IL-1β, in regulating αSyn levels in the gut [73].

### *6.2 Intracellular Accumulation of α-Synuclein*

When fluorescently labeled αSyn was applied to primary cultured mouse enteric neurons, intracellular uptake was observed, with αSyn concentrated in regions where FABP2 was localized [74]. FABP2 is a subtype of FABP family protein that is abundantly expressed in the intestine [75]. FABP3, another subtype of the FABP family expressed in the brain, plays a crucial role in αSyn pathology in the CNS [76]. Specifically, FABP3 has been implicated in the neuronal uptake of αSyn, its oligomerization, and its propagation within the brain [77–79]. Based on these findings, it is conceivable that, just as FABP3 plays a critical role in CNS αSyn pathology, FABP2 may be involved in the intracellular uptake, aggregation, and intercellular transmission of αSyn within the ENS.

In mice lacking leucine-rich repeat kinase 2 (*Lrrk2*), a known PD risk gene, αSyn accumulation in the colon was greater than that in the wild-type mice [80,81]. Although no significant differences were observed in the structure of enteric neurons or the proportions of major immune cell phenotypes, the number of biphenotypic cells expressing both the neuronal marker Hu C/D and the neural progenitor/glial marker Sox2 was increased.

### *6.3 Extracellular Secretion of α-Synuclein*

Knowledge of the mechanisms of extracellular secretion of αSyn from enteric neurons is limited. One study using primary cultured neurons from the rat embryonic small intestine demonstrated that, in enteric

neurons, αSyn is physiologically secreted via vesicle-mediated exocytosis that depends on the endoplasmic reticulum/Golgi apparatus, and that this secretion is regulated by neuronal activity [82].

## 7 Discussion

If the gut plays a crucial role in the onset of synucleinopathies, targeting the gut may offer a means of prevention or slowing the disease progression. One approach that has entered clinical trials involves the modulation of the gut microbiota. Specifically, dietary interventions, prebiotics, probiotics, and fecal microbiota transplantation have been explored, and the clinical trials related to these methods are comprehensively reviewed by Merchak et al. [83]. Furthermore, as discussed in this review, considering the involvement of inflammation and immune processes in gut αSyn pathology, interventions targeting pattern recognition receptors and cytokine signaling pathways may also be effective in preventing or slowing disease progression. To validate these possibilities, the need for large-scale randomized trials involving diverse populations has been emphasized [84].

Although no pharmacological treatments directly targeting the gut have been developed, further elucidation of the mechanisms of αSyn pathology in the ENS, as discussed in this review, may lead to the identification of novel molecular targets. However, the mechanisms of the ENS may differ significantly from those of the CNS. For example, as mentioned in the previous section, ENS and CNS neurons may respond differently to stimuli such as LPS treatment [73]. Moreover, it has been suggested that ENS cells may be partially resistant to acute degeneration induced by exposure to αSyn PFFs [85]. Additionally, enteric neurons are exposed to conditions such as gut microbiota alterations and gut inflammation, environments to which CNS neurons are not typically subjected.

Although this review examined αSyn pathology in the gut from several perspectives, our current understanding remains fragmented. Future research should integrate these findings to clarify the complex and intertwined mechanisms involved. Specifically, it is necessary to clarify whether the findings obtained from various animal models accurately reflect the condition of patients and which stage of the disease in patients these findings correspond to. To address this, studies using patient biopsy tissues and organoids may be useful. In addition, drug discovery research aimed at treatment and prevention is essential. By developing drugs that target the molecular mechanisms of intestinal αSyn pathology, which are gradually being elucidated, there is hope for the future development of therapies that enable early interventions.

## 8 Conclusion

In this review, we provide a brief comprehensive overview of the current knowledge on intestinal αSyn pathology from multiple perspectives, including pathological findings in patients, animal models, changes in the gut environment, and molecular mechanisms. These studies highlight the critical role of the gut in understanding the pathomechanisms of PD and DLB and in developing future therapeutic interventions. Moving forward, it is essential to bridge the gap between research based on animal models and cultured cells and clinical applications. To achieve this, fragmented information must be clarified comprehensively and systematically. Ultimately, this may lead to the development of therapies that enable early interventions. Research focusing on the gut holds the key to opening new avenues for understanding and treating LBD.

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