IBRO Neuroscience Reports 18 (2025) 384–388

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Phosphorylated alpha-synuclein distribution in the colonic enteric nervous system of patients with diverticular disease

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ARTICLE INFO

Keywords:
Enteric nervous system
Alpha-synuclein
Parkinson's disease
Diverticular disease
Intestinal inflammation

ABSTRACT

Background: Phosphorylated alpha-synuclein (P-aSyn) is a biomarker for Parkinson's disease (PD), with potential relevance in intestinal inflammatory disorders.
Objectives: This study examines the distribution of P-aSyn in colonic tissues of patients with diverticular disease (DD) compared to age-matched controls.
Methods: P-aSyn distribution was analyzed in colon samples of 45 patients with diverticulitis (D-itis), 12 with diverticulosis (D-osis), and 30 controls via immunohistochemistry.
Results: P-aSyn immunoreactivity was found along enteric neurons of the myenteric and submucosal plexus in 93.1 % of participants, with similar distribution across D-itis, D-osis, and controls. Elevated reactivity appeared in 16.7 % of D-osis, 19.6 % of D-itis, and 30.0 % of controls.
Conclusion: P-aSyn presence in colonic tissue did not significantly differ between DD patients and controls, suggesting that DD-related inflammation does not notably affect P-aSyn expression. Further research is warranted to explore aSyn roles within the enteric nervous system in intestinal inflammatory disorders and their relation with neurodegenerative diseases.

Introduction

Phosphorylated alpha-synuclein (P-aSyn) has emerged as a significant biomarker in the context of Parkinson's disease (PD) and related synucleopathies (Schneider et al., 2016). Recent research has expanded the scope of P-aSyn's relevance beyond the central nervous system. Indeed, expression of aSyn in phosphoralyted or unphosphorylated forms has been demonstrated within the enteric nervous system (ENS) (Schneider et al., 2016; Bu et al., 2020; Böttner et al., 2012). Conversely, important work has been performed to evaluate the potential of enteric P-aSyn has a biomarker for PD (Schneider et al., 2016; Corbillé et al., 2016, 2017; Lebouvier et al., 2008; Beach et al., 2010). Nonetheless, still little is known about the regulation of enteric aSyn phosphorylation and its implication in gastro-intestinal physiology (Paillusson et al., 2010).

Prevalence of intestinal inflammatory disorders, including inflammatory bowel diseases (IBD) is constantly increasing worldwide (Barbara et al., 2008). Accumulating evidence supports that intestinal inflammation modulates the response of the gut-brain axis to stress and may thus influence the progression and outcome of neurological disorders (Barbara et al., 2014). In particular, emerging evidence suggests that aSyn becomes aberrantly phosphorylated in the ENS during intestinal inflammation (Chan et al., 2022). Conversely, a link between intestinal inflammation and PD has been proposed and patients presenting with IBD have an higher risk to develop PD (Konings et al., 2023). PD has further been associated to chronic low-grade intestinal inflammation and to irritable bowel syndrome (Konings et al., 2023; Rolli-Derkinderen et al., 2020).

Noteworthy, diverticular disease (DD) has also been proposed to potentially be linked to PD (Macerollo et al., 2017; Zeng et al., 2022). DD involves the formation of pseudo-diverticula, which are small, bulging pouches that can form in the lining of the digestive system, particularly in the distal colon (Wedel et al., 2015). Pseudo-diverticula are widely present in elderly population and can remain undetected as long as no major inflammation takes place - a condition described as diverticulosis (D-osis). However, these pouches can become inflamed, leading to diverticulitis (D-itis) (Wedel et al., 2015). The association

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https://doi.org/10.1016/j.ibneur.2025.02.009
Received 4 December 2024; Received in revised form 12 February 2025; Accepted 20 February 2025
Available online 26 February 2025

between DD and PD is hypothesized to be related to chronic low-grade inflammation that may influence the phosphorylation status and pathological aggregation of aSyn (Macerollo et al., 2017; Zeng et al., 2022). Thus, characterization of aSyn pathology in the context of DD could provide valuable insights into the broader implications of gut health on neurodegeneration in PD.

In order to investigate a potential association between DD and synucleinopathies, we performed a systematic analysis of P-aSyn distribution in full-thickness colon specimens of patients with DD (D-osis and D-itis) and age-matched controls.

Methods

Control group and patients with diverticulosis

Segments of the sigmoid colon from 30 patients (mean age 70.8 y; 12 females, 18 males) who underwent partial colectomy for non-obstructive colorectal carcinoma were used as control samples. Patients with non-inflamed pseudodiverticula-affected sigmoid colon as incidental finding in the control group were collected as the diverticulosis (D-osis) group (n = 12, 5 females, 7 males, mean age: 71.0 y). Anorectal evacuation disorders had been ruled out beforehand. Full-thickness specimens were collected at a safe distance (> 5 cm) from the tumor and promptly transferred to the laboratory for tissue processing.

Patients with diverticulitis

For patients with diverticulitis (D-itis), sigmoid colon specimens were collected from 45 D-itis (mean age 59.6 y; 31 females, 14 males) who underwent sigmoid resection or left hemicolectomy for symptomatic D-itis as previously reported (Cossais et al., 2019a, 2019b). DD history was documented in form of a self-reported questionnaire. Surgery was carried out electively during symptom-free intervals. Regions with altered colonic wall anatomy due to transmural mucosal/submucosal outpouchings or evidence of fibrotic scarring were excluded from tissue sampling. One individual with D-itis and additional anorectal outlet obstruction was furthermore included in the study. The study was approved by the Local Ethics Committee of the Faculty of Medicine, Kiel University, Germany (B299/07).

Retrieval and processing of substantia nigra specimens

Substantia nigra tissue was obtained post-mortem from two body donors with diagnosed PD (1 male, 1 female, age range: 81–92 y), as well as from one control individual without known neurological manifestation (male, 88 y), who were recruited from the body donation program of the Institute of Anatomy, Kiel University, in compliance with the Local Ethics Committee of the Faculty of Medicine, Kiel University, Germany (D512/24).

Immunohistochemistry

After surgical removal, colon specimens were transferred into phosphate-buffered saline (pH 7.2). Full-thickness rectangular tissue blocks (30 mm ×10 mm) were pinned out flat on a cork plate by fine needles for fixation (4 % paraformaldehyde in phosphate-buffered saline) for 24 hours. After dehydration, tissue blocks were transferred into paraffin wax and cut into orthogonal sections (6 µm) along the longitudinal gut axis for immunohistochemistry.

Immunohistochemical staining was performed in accordance with a standard protocol (Cossais et al., 2021). Briefly, after deparaffinization in xylol and rehydration in alcohol with descending concentrations, tissue sections were pretreated with citrate buffer (pH 6.0, 95°C, water bath) for 25 minutes, followed by overnight incubation with rabbit-anti-phosphorylated alpha-synuclein antibody (1/1000, D1R1R, Cell signaling Technology) in antibody diluent (Thermo Fisher Scientific, Carlsbad, USA). After washing with PBS, the sections were incubated for one hour with the BrightVision 1 step detection system anti-rabbit HRP (ImmunoLogic). Immpact DAB EqV was used as substrate for HRP (Vector Laboratories). Nuclei were counterstained with hematoxylin. To correct for unspecific signals, blank controls were performed by omitting the primary antibody. Images were acquired using a Leica Aperio CS2 slide scanner or a Keyence BZ-x810e inverted microscope.

Quantification of P-aSyn immunohistochemical signals

Scanned images were visualized using the Aperio ImageScope software (version 12.4.6.5003, Leica). Presence of P-aSyn immunoreactive signal and signal intensity was evaluated by two trained experts (F.C. and M.H.) and classified using a three-point semi-quantitative scale: negative (0), mild positivity (+), strong positivity (++).

Statistical analyses

Prism GraphPad version 9.0 and SPSS version 29 were used for statistical analysis. Differences between DD and control groups for categorical variables were assessed with the Chi-square test. Test results with a p-value < 0.05 were considered statistically significant. Spearman's rank correlation (two-sided) was applied for analyses of correlations.

Results

A total of 88 individuals were included in the study. Control, D-osis und D-itis groups were comparable regarding age (age range: 42–90 y, p = 0.42), whereas female to male ratio was higher in the D-itis group (p = 0.008) (Table 1).

Immunohistochemistry was used to characterize the distribution of P-aSyn in full-thickness colonic specimens of control, D-itis and D-osis individuals. The P-aSyn antibody (D1R1R) was first characterized on post-mortem nigral tissues of two body donors with PD and one control donor without known neurological diseases, showing clear detection of nigral Lewy bodies and Lewy neurites in PD subjects (Fig. 1 B).

A semi-quantitative approach was used to evaluate the distribution of P-aSyn on colonic tissue. Overall, positive P-aSyn staining was observed in all groups ranging from 91.3 % (D-itis), 93.1 % (control) to 100 % (D-osis) (Table 1). Presence of P-aSyn was not significantly different between males and females (p = 0.557) or in the different age categories (41–60 y: 89.6 %, 61–80 y: 96.2 %, 81–100 y: 99.2 %, p = 0.262). In control subjects, P-aSyn immunoreactivity was observed within ganglia of the myenteric plexus (MP) in 24 (80.0 %) individuals and ganglia of the sub-mucosal plexus (SMP) in 22 (73.3 %) individuals with 30.0 % showing high immunoreactive level. Distribution pattern observed in D-itis and D-osis did not significantly differ from the control group. P-aSyn was detected within ganglia of the MP and SMP in respectively 91.7 % and 66.7 % of D-osis individuals as well as in respectively 73.9 % and 82.6 % of D-itis patients (Table 1, Fig. 1 A).

Table 1
Comparison of Age, Gender Distribution, and P-aSyn Immunoreactivity Across Control, Diverticulosis (Dose), and Diverticulitis (Ditis) Cohorts. P-aSyn IR: phosphorylated alpha-synuclein immunoreactivity.

	control	Dose	Ditis	P value
number	30	12	46	
mean age	70.8	71	59.8	0.499
Males / females	18/12	7/5	14/32	0.029
P-aSyn IR	2 (6.7)	0 (0.0)	4 (8.7)	0.557
absent	19 (63.3)	10 (83.3)	33 (71.7)	0.393
mild	9 (30.0)	2 (16.7)	9 (19.6)	1.0
strong	28 (93.3)	12 (100)	42 (91.3)	0.557
pos. total				

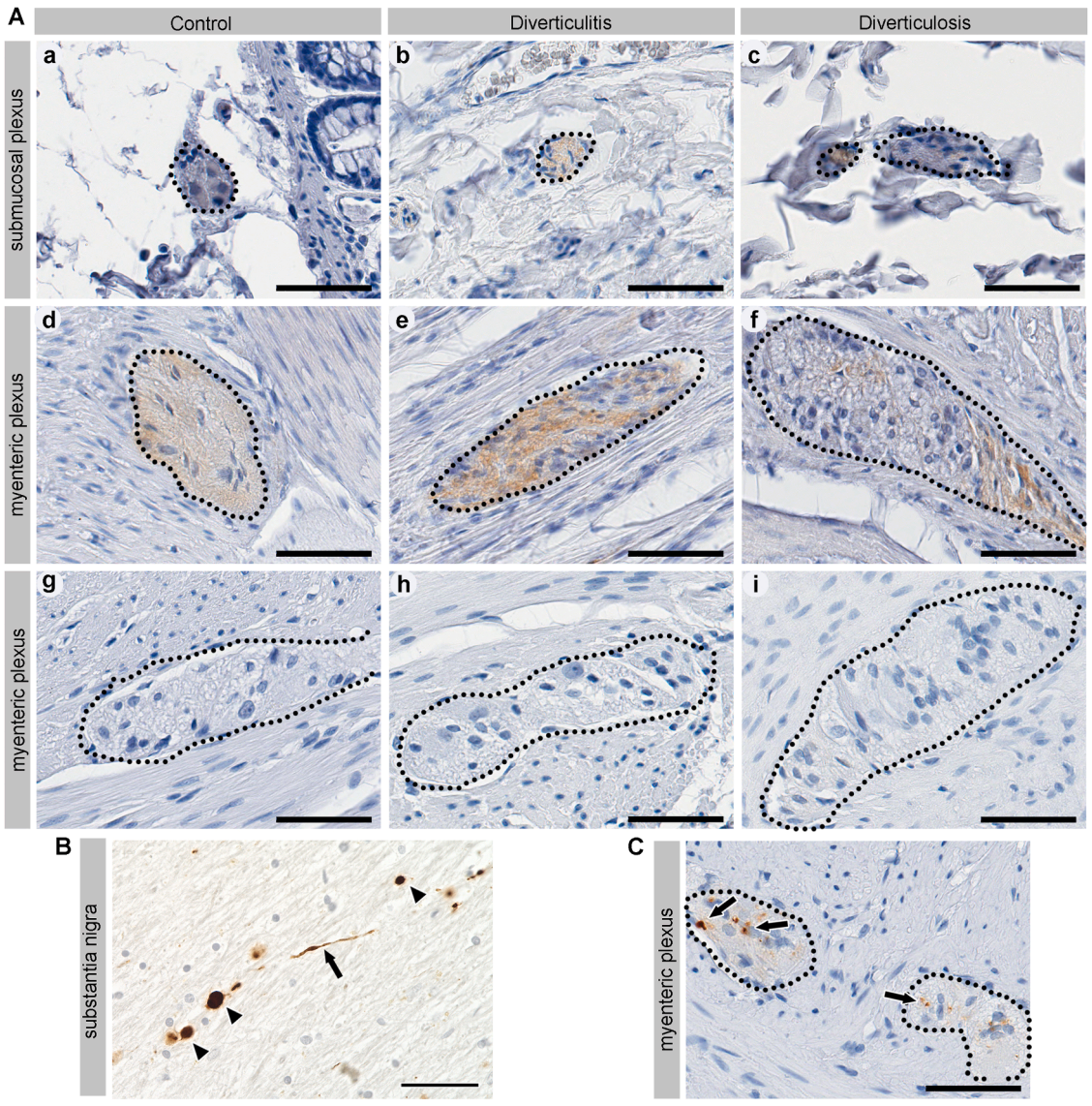

Fig. 1. A. Distribution pattern of P-aSyn in the colon of patients with diverticular disease (DD) and control individuals. Immunohistochemistry for P-aSyn was performed on colon specimens of control individuals (a, d, g), patients with diverticulitis (b, e, h) and patients with diverticulosis (c, f, i). No-immunoreactive myenteric ganglia are also shown (g, h, i). Black dotted lines delineate the ganglionic structures. Scale bar = 60 μm. **B.** Distribution pattern of P-aSyn in the substantia nigra of a PD patient. Immunohistochemistry for P-aSyn was performed on sections of the substantia nigra of a PD patient. Pathological accumulation of P-aSyn in Lewy bodies (arrowheads) and Lewy neurites (arrow) is observed. Scale bar = 60 μm. **C.** P-aSyn immunoreactive Lewy neurite-like deposits (arrows) were observed in the submucosal (a) and myenteric (b) plexus of a patient with diverticulitis additionally presenting with anorectal outlet obstruction. Scale bar = 60 μm.

Distribution of P-aSyn staining was highly variable even within individual ganglia, with some enteric neurons presenting strong immunoreactive signal, while other neurons remained negative for P-aSyn (e.g. Fig. 1 A(f)). Strong P-aSyn immunoreactive levels were observed in 16.7 % of D-osis patients, 19.6 % of D-itis and 30.0 % of control individuals (Table 1). P-aSyn-positive Lewy neurite-like aggregates were observed in one patient with D-itis presenting with anorectal outlet obstruction but in none of the other patients with D-itis, D-osis and control subjects (Fig. 1 C).

Discussion

Numerous studies have analyzed the distribution of aSyn and its phosphorylated form in GI tissues. The absence of standardization and limited specificity of available assays have led to conflicting results regarding the potential use of enteric P-aSyn as a diagnostic biomarker for synucleopathies (Schneider et al., 2016). Furthermore, specificity of P-aSyn antibodies varies according to post-translational modifications and protein truncations which likely take place within intestinal tissues (Lashuel et al., 2022). While Lewy bodies and P-aSyn immunoreactive neurites have been observed in intestinal tissues of PD patients (Barrenschee et al., 2017), aSyn has been also reported within the human ENS under physiological conditions both in its native and phosphorylated forms (Bu et al., 2020; Böttner et al., 2012; Barrenschee et al., 2017).

Using an antibody previously validated on cultured enteric neurons using Western-blot (Lassozé et al., 2022), we confirm the frequent presence of P-aSyn within the colon of both control individuals and DD patients. However, P-aSyn distribution in intestinal tissues was highly variable among the analyzed individuals and even within individual enteric ganglia. While some tissues exhibited significant P-aSyn accumulation, others showed minimal to complete absence of immunoreactivity independently of the disease state.

Furthermore, P-aSyn distribution was not significantly altered in D-

itis nor D-osis subjects compared to controls. We further failed to observe any significant correlation between P-aSyn distribution and increased age. These results contrast with previous data from our group and others which had suggested an higher accumulation of P-aSyn in aged individuals (Bu et al., 2020; Böttner et al., 2012). This observation may be due to the fact that only elderly individuals were evaluated in the present study, whereas younger subjects (age < 40 years) were included in previous reports.

The observed variability in P-aSyn detection suggests that its accumulation in intestinal tissues may be influenced by multiple cellular and environmental factors, which remain to be identified. Previous studies also reported variable P-aSyn immunoreactivity along the GI tract both in control individuals and in patients with PD (Jotanovic et al., 2022; Hilton et al., 2014; Yan et al., 2018). Similarly, contrasting reports have been published regarding aSyn expression in IBD. Whereas aSyn has been shown to be increased in the ENS of patients with Crohn's disease but not in patients with ulcerative colitis (UC) (Prigent et al., 2019), another study has reported increased P-aSyn in the ENS of patients with UC (Espinosa-Oliva et al., 2024). Nonetheless, presence of enteric aSyn pathology appears to be a rare condition in IBD (Shannon et al., 2012; Gibo et al., 2022; Aldecoa et al., 2015). It is noteworthy that the only case of enteric Lewy pathology observed in our study presented with anorectal outlet obstruction. A potential link between enteric P-aSyn deposits and this disorder should be investigated in further studies.

The limitations of this study should be acknowledged. The characterization of aSyn must be further expanded to encompass the identification of pathological conformers using conformation-specific antibodies or seeding amplification assays (Skorvanek et al., 2018; Fenyi et al., 2019). Moreover, potential confounding factors, such as lifestyle habits and medication, may influence enteric P-aSyn regulation and should be systematically accounted for in future investigations. Intestinal disorders have been implicated in the dysregulation of additional neurodegenerative markers, including tau and amyloid deposits, which similarly should be evaluated in the context of DD and ageing (Lionnet et al., 2018; Grillo et al., 2022; Bissacco et al., 2024).

Together, these observations underline the complexity of aSyn distribution within the GI tract. In particular, future studies should aim at identifying the factors modulating aSyn phosphorylation within the ENS and clarify its potent role in gastrointestinal disorders as well as its link to intestinal inflammation. Exploring the molecular mechanisms driving aSyn aggregation in the periphery could uncover novel therapeutic targets for mitigating non-motor symptoms in PD.

Ethical Compliance Statement

The study was approved by the Local Ethics Committee of the Faculty of Medicine, Kiel University, Germany (B299/07) and (D512/24). All participants and body donors have given written informed consent prior to the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest

F.C. received funding from the Faculty of Medicine, Kiel University (intramural research grant K126422). The authors declare that there are no conflicts of interest relevant to this work. Open Access funding enabled and organized by Projekt DEAL.

CRediT authorship contribution statement

Wedel Thilo: Writing – review & editing, Resources, Project administration, Methodology, Conceptualization. **Richter Florian:** Writing – review & editing, Resources. **Lucius Ralph:** Writing – review & editing, Resources. **Schröder Katja:** Writing – review & editing, Formal analysis, Data curation. **Egberts Jan-Hendrik:** Writing – review & editing, Resources. **Böttner Martina:** Writing – review & editing, Resources, Conceptualization. **Hörnke Marie Christin:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Cossais François:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank Katrin Masuhr, Lisa Behnke and Dagmar Lukas (Institute of Anatomy, Kiel University) for expert technical assistance.

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