Ullah *et al. Ageing Neur Dis* 2023;3:5
DOI: 10.20517/and.2023.07

Ageing and Neurodegenerative Diseases

Commentary

Open Access

A new Perspective on Parkinson's disease: exploring the involvement of intestine and vagus lysates in α-synucleinopathy propagation

Rahat Ullah[1,2], Valina L. Dawson[1,2,3,4], Ted M. Dawson[1,2,3,5]

[1]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
[2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
[3]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
[4]Department of Physiology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
[5]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

Correspondence to: Ted M. Dawson, MD, PhD, Institute for Cell Engineering, Johns Hopkins University School of Medicine, 733 North Broadway, MRB 731, Baltimore, MD 21205, USA. E-mail: tdawson@jhmi.edu

How to cite this article: Ullah R, Dawson VL, Dawson TM. A new Perspective on Parkinson's disease: exploring the involvement of intestine and vagus lysates in α-synucleinopathy propagation. *Ageing Neur Dis* 2023;3:5. https://dx.doi.org/10.20517/and.2023.07

Received: 7 Mar 2023 **First Decision**: 27 Mar 2023 **Revised**: 29 Mar 2023 **Accepted:** 29 Mar 2023 **Published:** 29 Mar 2023

Academic Editor: Weidong Le **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

In Parkinson's disease (PD), the accumulation of misfolded α-synuclein (α-syn) in the brain is a major characteristic of the pathology. α-Syn formation and aggregation may originate in the enteric nervous system and pathologic α-syn can be transmitted to the central nervous system via the vagus nerve. In this commentary, we summarize the findings of Yang *et al.*[1] in which they report on the ability of a Parkinson's disease patient's intestinal and vagus lysates containing pathologic α-syn to template endogenous rat α-syn culminating in the spread of pathologic α-syn, deposition of pathologic α-syn, and neuroinflammation in different brain regions and neurodegeneration of dopamine neurons. These observations are discussed with other studies supporting the significance of the gastrointestinal system in PD pathogenesis and future directions of research are highlighted.

Keywords: Parkinson's disease (PD), Enteric nervous system, α-Synuclein (α-syn), Vagus nerve, Neurodegeneration, pathologic α-syn, Neuroinflammation.

Synucleinopathies encompass a range of neurodegenerative disorders, including Parkinson's disease (PD) that is characterized by loss of dopaminergic neurons in the substantia nigra (SN) and the presence of Lewy bodies /Lewy neurites in the central and peripheral nervous system[2-4]. While PD is primarily recognized as a movement disorder, it is now understood that the symptoms extend beyond motor dysfunction, as individuals with PD frequently experience non-motor symptoms, particularly gastrointestinal dysfunction[5]. There is a growing focus on the role of the GI tract and the enteric nervous system (ENS) in the onset and progression of PD[6]. The ENS is a network of neurons located in the GI wall that plays a crucial role in the bidirectional communication system between the CNS and the GI tract, known as the gut-brain axis. According to the hypothesis proposed by Braak *et al.*[7], α-syn pathology may have its origins in the ENS and propagates to the brain through autonomic nerves. In support of this notion, truncal vagotomy reduced the risk of PD in humans by 40%-50% after a follow-up period of 10-20 years[8,9]. Additionally, the autonomic peripheral nervous system (PNS) has been found to deteriorate years before the nigrostriatal dopamine system in some PD patients[10].

It is hypothesized that pathological α-syn species spreads in a prion-like manner from one cell to another through templated misfolding and/or aggregation of nascent or properly configured α-syn, which is then transmitted to adjacent cells[11,12]. Studies support the transcellular spread of pathological α-syn through the demonstration that PD-like Lewy pathology can be induced in animals by injecting synthetic α-syn fibrils into different brain regions[11,13], or by injecting pathological α-syn species[14,15] from transgenic mice or patients with synucleinopathies into animal brains, leading to the propagation of α-syn pathology. Likewise, Yang *et al.*[1] investigated the transmission of pathologic α-syn from a pathologically verified PD case to rats by injecting intestinal or vagus lysate directly into rat brains. Results showed that these lysates contained pathologic α-syn, which led to the formation of Lewy body-like inclusions in the substantia nigra (SN) and striatum (STR) of the recipient rats [Figure 1]. Additionally, the injection prompted the accumulation of α-syn aggregates across numerous brain regions, including the substantia nigra, striatum, brain stem, cortex (somatosensory and frontal), cerebellum, and hypothalamus, eventually resulting in the neurodegeneration of nigrostriatal dopaminergic neurons on both sides of the brain [Figure 1]. The findings of this study are largely in line with those of prior research, including Thomzig *et al.*'s demonstration that injecting homogenized brain and stomach wall samples from individuals with PD can trigger α-syn aggregation[16]. Additionally, Recasens *et al.* found that injecting LB extracts from PD patients into the brains of wild-type mice and macaques caused the development of α-syn pathology and degeneration of the nigrostriatal system[14]. Recent reports also observed α-syn aggregates in the ENS and vagus nerve. In rodent models, injecting pre-formed α-synuclein fibrils into sympathetic ganglia or duodenum muscle layers can cause α-syn deposition and propagation[17-19]. In contrast, Prusiner *et al.* reported that the transmission of homogenates from brains affected by PD did not lead to the development of abnormal α-synuclein inclusions in transgenic mice, demonstrating the complex and heterogeneous nature of neurodegenerative diseases[20]. In summary, while the results of the current study align with previous research, the intricate nature of neurodegenerative disorders highlights the need for continued investigation to gain a comprehensive understanding of the role of transmission of pathologic α-syn and its contributions to the progression of PD.

Although the current study showed that pathologic α-syn species exist in the intestines and vagus nerve of a PD patient and that they can induce prion-like propagation of α-syn pathology in rats, they have some

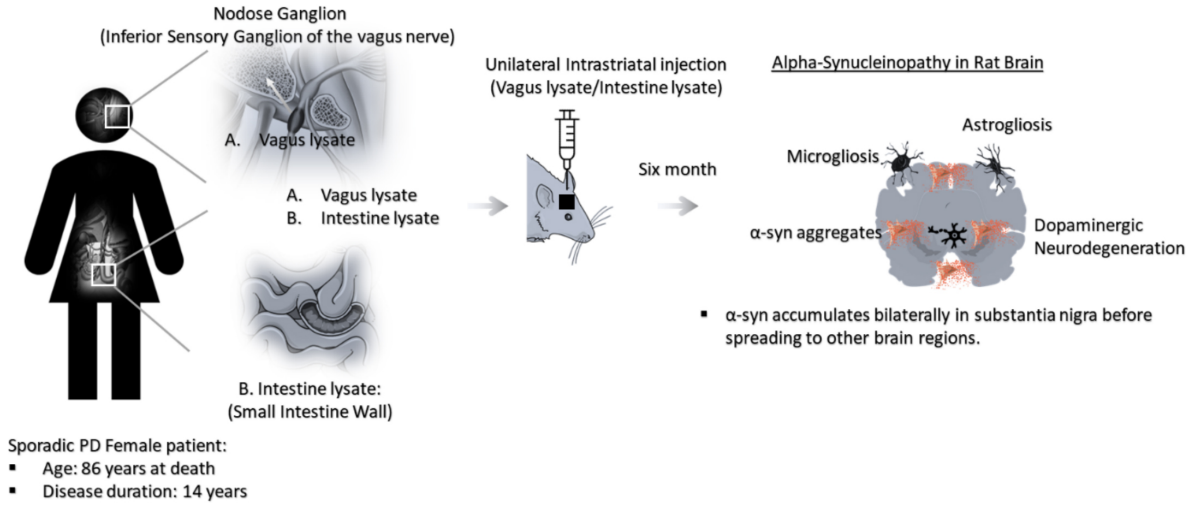

Figure 1. Experimental timeline and outcomes of rats that were injected with intestine lysate or vagus lysate obtained from an individual with PD, demonstrating the accumulation of human α-synuclein in the substantia nigra and other brain regions, activation of microglia and astrogliosis, loss of dopaminergic neurons, and propagation of pathological α-synuclein in bilateral brain regions.

notable limitations. The study found that injecting lysates from a single PD patient's intestine and vagus induced α-syn pathology in rats, but this unilateral approach may not accurately reflect the bilateral nature of PD in humans. Similarly, the study also lacked lysates from non-PD individuals of the same age as controls and used lysates from only one PD patient, limiting the generalizability of the results. Therefore, these findings should be validated through further research with bigger sample sizes and additional replications. Another limitation of this research article is the lack of *in vitro* studies. In vitro models may have limitations in terms of physiological relevance compared to *in vivo* studies. However, they have been useful tools in investigating the mechanisms (exocytosis, axonal transport, tunneling nanotubes, endocytosis, and direct penetration) of intercellular transfer and seeding properties of pathologic α-syn. As such, the inclusion of *in vitro* studies in this research could have provided a more comprehensive understanding of the topic at hand. Further research that incorporates *in vitro* models may help to overcome this limitation and provide a more complete picture of the mechanisms underlying the initiation and spread of α-synucleinopathy in the brain. Finally, HPLC analysis was only performed on the intestine lysate group, not the vagus group. Notably, these limitations do not diminish the importance of the research, but further studies may be needed to provide a more complete picture of the disease.

The findings of this study hold potential importance for the field of PD research. The identification of the intestine and vagus as sources of pathologic α-syn that can propagate disease pathology is a novel finding that opens up new avenues of research. The study's findings on the prion-like propagation of α-syn aggregates in non-CNS tissues and their transmission to the brain have significant implications for future research in the field of PD. The future directions stemming from this study, such as investigating the nerve cell types that are vulnerable and the transmission mechanisms, as well as investigating potential safeguards to prevent the propagation of α-syn aggregates, have important implications for the development of effective therapies for PD. Overall, this study's novel findings and future directions provide a foundation for advancing our understanding of PD pathogenesis and developing new therapeutic strategies to enhance the quality of life for individuals with PD.

DECLARATIONS

Authors' contributions

Wrote the first draft of the commentary: Ullah R
Edited and contributed to the final draft: Dawson VL, Dawson TM

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by grants from the JPB Foundation, the Farmers Family Foundation and the MJFF ASAP grant to Dawson TM.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate.

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Yang Z, Wang Y, Wei M, et al. Intrastriatal injection of Parkinson's disease intestine and vagus lysates initiates α-synucleinopathy in rat brain. *Cell Death Dis* 2023;14:4. DOI PubMed PMC
2. Pirooznia SK, Rosenthal LS, Dawson VL, Dawson TM. Parkinson disease: translating insights from molecular mechanisms to neuroprotection. *Pharmacol Rev* 2021;73:33-97. DOI PubMed
3. Sacino AN, Brooks M, McKinney AB, et al. Brain injection of α-synuclein induces multiple proteinopathies, gliosis, and a neuronal injury marker. *J Neurosci* 2014;34:12368-78. DOI PubMed PMC
4. Van Den Berge N, Ferreira N, Gram H, et al. Evidence for bidirectional and trans-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats. *Acta Neuropathol* 2019;138:535-50. DOI PubMed PMC
5. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:10-5. DOI PubMed
6. Klingelhoefer L, Reichmann H. Pathogenesis of Parkinson disease--the gut-brain axis and environmental factors. *Nat Rev Neurol* 2015;11:625-36. DOI PubMed
7. Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm (Vienna)* 2003;110:517-36. DOI PubMed
8. Liu B, Fang F, Pedersen NL, et al. Vagotomy and Parkinson disease: a Swedish register-based matched-cohort study. *Neurology* 2017;88:1996-2002. DOI PubMed PMC
9. Svensson E, Horváth-Puhó E, Thomsen RW, et al. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 2015;78:522-9. DOI PubMed
10. Van Den Berge N, Ferreira N, Mikkelsen TW, et al. Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats. *Brain* 2021;144:1853-68. DOI PubMed PMC
11. Paumier KL, Luk KC, Manfredsson FP, et al. Intrastriatal injection of pre-formed mouse α-synuclein fibrils into rats triggers α-synuclein pathology and bilateral nigrostriatal degeneration. *Neurobiol Dis* 2015;82:185-99. DOI PubMed PMC
12. Freundt EC, Maynard N, Clancy EK, et al. Neuron-to-neuron transmission of α-synuclein fibrils through axonal transport. *Ann Neurol* 2012;72:517-24. DOI PubMed PMC
13. Abdelmotilib H, Maltbie T, Delic V, et al. α-Synuclein fibril-induced inclusion spread in rats and mice correlates with dopaminergic Neurodegeneration. *Neurobiol Dis* 2017;105:84-98. DOI PubMed PMC
14. Recasens A, Dehay B, Bové J, et al. Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. *Ann Neurol* 2014;75:351-62. DOI PubMed
15. Bernis ME, Babila JT, Breid S, Wüsten KA, Wüllner U, Tamgüney G. Prion-like propagation of human brain-derived alpha-synuclein in transgenic mice expressing human wild-type alpha-synuclein. *Acta Neuropathol Commun* 2015;3:75. DOI PubMed PMC

16. Thomzig A, Wagenführ K, Pinder P, Joncic M, Schulz-Schaeffer WJ, Beekes M. Transmissible α-synuclein seeding activity in brain and stomach of patients with Parkinson's disease. *Acta Neuropathol* 2021;141:861-79. DOI PubMed PMC
17. Wang XJ, Ma MM, Zhou LB, et al. Autonomic ganglionic injection of α-synuclein fibrils as a model of pure autonomic failure α-synucleinopathy. *Nat Commun* 2020;11:934. DOI PubMed PMC
18. Ulusoy A, Rusconi R, Pérez-Revuelta BI, et al. Caudo-rostral brain spreading of α-synuclein through vagal connections. *EMBO Mol Med* 2013;5:1119-27. DOI PubMed PMC
19. Kim S, Kwon SH, Kam TI, et al. Transneuronal Propagation of Pathologic α-Synuclein from the Gut to the Brain Models Parkinson's Disease. *Neuron* 2019;103:627-641.e7. DOI PubMed PMC
20. Prusiner SB, Woerman AL, Mordes DA, et al. Evidence for α-synuclein prions causing multiple system atrophy in humans with parkinsonism. *Proc Natl Acad Sci USA* 2015;112:E5308-17. DOI PubMed PMC