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Citation for published version:

Digital Object Identifier (DOI):
10.1002/mds.27556

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Movement Disorders

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Gut–Brain Axis and the Spread of α-Synuclein Pathology: Vagal Highway or Dead End?

David P. Breen, MBChB, PhD, Glenda M. Halliday, PhD, and Anthony E. Lang, MD

1Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, Scotland
2Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, Scotland
3Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland
4Brain and Mind Centre, Sydney Medical School, University of Sydney, Camperdown, Australia
5School of Medical Sciences, University of New South Wales, Kensington, Australia
6Neuroscience Research Australia, Randwick, Australia
7Edmond J. Safra Program in Parkinson’s Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Canada
8Krembil Research Institute, Toronto Western Hospital, Toronto, Canada

ABSTRACT: Spread of α-synuclein pathology from the peripheral to central nervous system may be an important etiological factor in Parkinson’s disease, although there are some unanswered questions about its correlation with neuronal loss. Experimental evidence has highlighted the gastrointestinal tract as a potential starting point for aggregated α-synuclein, with the vagus nerve acting as a “highway” by which pathology may be transmitted to the lower brain stem. This review begins by highlighting the key studies demonstrating that α-synuclein pathology has the ability to spread from certain sites in the gastrointestinal tract to the brain (and vice versa). We go on to assess the recent epidemiological studies that have shown that vagotomy and appendectomy may have the potential to reduce the risk of developing Parkinson’s disease. Finally, we discuss the factors in the gastrointestinal tract (such as dysbiosis of the gut microbiota, infection, and inflammation) that may trigger α-synuclein aggregation in the first place, as well as other potential mechanisms underlying the distribution of α-synuclein pathology in the brain. © 2019 International Parkinson and Movement Disorder Society

Key Words: α-synuclein; gut; peripheral; prion; vagus nerve

The synaptic protein α-synuclein is the principal component of Lewy bodies and Lewy neurites, which are the neuropathological hallmarks of Parkinson’s disease (PD).1 The toxic aggregation of misfolded α-synuclein within these inclusions is a key pathological process in PD. However, the cause(s) of the conformational alteration of α-synuclein, and the mechanisms behind its distribution throughout the central and peripheral nervous systems, remain unknown.

Damage to specific subregions of the substantia nigra pars compacta (SNc) is central to the cardinal motor features of PD, but extensive extra-nigral pathology is well recognized in PD. In autopsy studies of confirmed Lewy body cases, α-synuclein aggregation has been observed in the spinal cord and peripheral nervous system (paravertebral sympathetic ganglia, vagus nerve, gastrointestinal [GI] tract, heart, and other organs more variably).2,3

The original Braak staging system for PD proposed that synucleinopathy begins in the anterior olfactory nucleus and the dorsal motor nucleus of the vagus nerve (DMNV).4 In the GI tract, a pathogen or other exposure could potentially trigger α-synuclein aggregation after gaining access to the nervous system through axons of the myenteric (Auerbach’s) plexus and/or the submucosal (Meissner’s) plexus via postganglionic neurones.5 Indeed, α-synuclein aggregates have been
reported in these neurons in PD patients, with studies in mice showing that aggregation is more abundant in aged animals. Theoretically, pathology could therefore reach preganglionic parasympathetic motor neurons of the vagus nerve via trans-synaptic transmission, before being transported to the lower brain stem via retrograde axonal transport.

This review assesses the evidence relating to the spread of pathology from the GI tract to the brain, with particular reference to the vagus nerve, which has been the main focus of research to date (Fig. 1). We also outline the importance of these findings for our understanding of PD pathogenesis and suggest research priorities for the future.

**Gut–Brain Axis in PD**

Constipation, commonly caused by autonomic dysfunction, is one of the most common nonmotor symptoms in PD. Aside from being a troublesome symptom for many patients, pooled analysis of epidemiological studies has suggested that constipation modestly increases the risk of developing PD, with phosphorylated α-synuclein being demonstrated in the GI tract up to 20 years before the onset of PD motor symptoms. In patients with established Lewy body disease, a rostro-caudal gradient of α-synuclein pathology in the GI tract has been reported, possibly relating to the known distribution of vagal innervation. A notable exception is the upper esophagus, in which no α-synuclein was detected in a recent study. This may be a result of the fact that although most of the vagal innervation of the GI tract is derived from neuronal cell bodies located in the DMNV, the cell bodies giving rise to the vagal innervation of the upper esophagus arise in the nucleus ambiguus (which is rarely affected in PD).

In addition, converging lines of evidence have emerged to suggest that α-synuclein pathology can be transmitted in a cell-to-cell fashion. So could α-synuclein pathology start in the GI tract and spread to the brain?

Animal experiments have provided some evidence to support this view. In one early study, chronic intragastric injection of rotenone (a pesticide that inhibits complex I of the mitochondrial respiratory chain) initiated α-synuclein accumulation in the enteric nervous system that subsequently spread to the DMNV and SNc, with accompanying selective dopaminergic cell loss. These alterations occurred without detectable levels of pesticide in the blood or brain and no inhibition of complex I activity in muscle or brain, arguing against systemic effects of rotenone being the cause for the observed changes. In a follow-up paper where rotenone-treated mice were pretreated with hemigagomony, the development of motor deficits was delayed and PD pathology was reduced in the DMNV and SNc.

Recently, injection of PD patient-derived brain lysate into the intestine of rats led to α-synuclein immunoreactivity in the intestinal wall and later the vagus nerve in a time-dependent manner. A similar result was seen after injecting recombinant α-synuclein (either monomeric, oligomeric, or fibrillar forms). However, no evidence of cell death in the DMNV or higher brain regions was demonstrated. Parallel studies in rats and nonhuman primates using viral vectors or preformed fibril injections into the GI tract further showed that peripheral pathology was sufficient to cause GI dysfunction but without sustained spread of pathology.

Ulusoy and colleagues took a different experimental approach to investigate the spread of pathology. Aden-associated viruses carrying DNA for human α-synuclein were injected unilaterally into the rat vagus nerve in the neck directly, which resulted in protein overexpression in the medulla oblongata. There was subsequent spreading of human α-synuclein to the pons, midbrain, and forebrain. This study supported the possibility that spread of α-synuclein from the periphery may trigger subsequent CNS disease. In a more recent paper, the same group showed that spread can also occur in the opposite direction. Using a similar method, they demonstrated that viral vector-mediated midbrain overexpression of human α-synuclein in rats led to accumulation of exogenous protein in vagal terminals of the stomach wall. The authors concluded that cholinergic neurons of the DMNV and their efferent projections—both of which were shown to contain human α-synuclein—represent a key relay center for the central-to-peripheral spread of α-synuclein pathology (and vice versa).

**Vagus Nerve in the GI Tract**

The vagus nerve, the main contributor to the parasympathetic nervous system, is the 10th cranial nerve and originates in the medulla oblongata. Within the medulla, the cell bodies of vagal fibres are found in the nucleus ambiguus and DMNV. These nuclei supply the efferent (motor) fibres of the vagus nerve to the rest of the body. Just distal to the jugular foramen, the nodose ganglion separately collects afferent (sensory) vagal innervation from visceral organs, projecting to the nucleus of the solitary tract to regulate cardiovascular, respiratory, and GI functions.

Upon descending and entering the abdominal cavity, medical students continue to be taught that the posterior or “right” vagus nerve supplies the proximal posterior stomach, spleen, small intestine, and large intestine as far as the splenic flexure. In fact, this nerve receives fibres from both right and left cervical vagus nerves. Similarly, the anterior or “left” vagus nerve (which supplies the anterior stomach, pylorus, proximal duodenum, and pancreas) receives fibres from both right and left cervical
vagus nerves. This means that any asymmetry of PD pathology in the brain stem cannot readily be used as an indicator of peripheral Lewy body burden in the GI tract, although previous studies have shown no evidence of such laterality anyway. Parts of the large intestine (distal one-third of the transverse colon, descending colon, sigmoid colon, and rectum) receive additional parasympathetic innervation through the pelvic splanchnic nerve (S2-4), which terminates in the pelvic plexus and emerges as the colonic and rectal nerve.
Among other things, the vagus nerve controls gut motility and acid secretion in the stomach. Prior to the widespread availability of proton pump inhibitors, resection of a 1 to 2 cm section of the vagus nerve (technically a “vagectomy,” but more commonly known as a vagotomy) was the treatment of choice for patients with peptic ulcer disease. The extent of vagotomy differs considerably depending on the level of transection; truncal vagotomy involves resection of the large anterior and posterior vagal nerve trunks as they enter the abdomen and denervates the stomach and eliminates all vagal function in the remainder of the abdominal cavity; selective vagotomy involves resection of the nerves innervating the entire stomach; and highly selective vagotomy involves resection of the nerves innervating the stomach body while preserving innervation to the antrum and pylorus.

Vagotomy and PD

If the vagus nerve is indeed a major route for α-synuclein propagation, vagotomy might be expected to be protective against the development of PD. In addition to the study from Pan-Montojo and colleagues in mice, several human epidemiological studies have looked at this (Table 1). A recent Swedish study used several nationwide registries to compare the risk of developing PD in patients who underwent vagotomy (n = 9430) when compared with age- and sex-matched controls (n = 377,200).24 Surgical codes were reviewed by a gastroenterologist before classifying vagotomy cases as truncal or selective (the latter incorporating both selective and highly selective types). Overall, vagotomy did not protect against PD. However, when cases were restricted to those diagnosed >5 years after the date of surgery, those with truncal (but not selective) vagotomy did have a lower risk (hazard ratio, 0.59; 95% confidence interval, 0.37-0.93). There was also a nonsignificant trend toward lower risk at >10 years and >20 years in this group. These analyses were adjusted for multiple comorbidities, including diabetes (which is known to increase the risk of PD but has been shown to be less common following vagotomy).25

These findings built on a previous population-based cohort study in Denmark that found that “truncal” vagotomy reduced the risk of PD >5 years after surgery by 15% when compared with the general population.26 This result was statistically non-significant, although a stronger effect was noted when analysis was restricted to >20 years (hazard ratio, 0.53; 95% confidence interval, 0.53-0.99). There was also a trend toward a lower risk of PD in the “truncal” vagotomy group when compared with the highly selective vagotomy group. Of note, because of the concerns about registry code validity, the “truncal” vagotomy group in this study included patients with both truncal and selective vagotomies requiring pyloroplasty.

Both of these studies concluded that the retained ability of α-synuclein to spread from certain GI sites to the brain stem via an intact vagus nerve might explain the lack of protective effect in those undergoing less extensive vagotomy procedures. Although this is an attractive hypothesis, there are several issues that require scrutiny. Most important, the number of incident PD cases in the vagotomy groups were small (approximately 100 in each of the

| Table 1. Epidemiological studies investigating vagotomy and subsequent PD risk |
|---------------------------|---------------------------|---------------------------|---------------------------|
| Author | Country | Number | Classification | Year of vagotomy | Number | Key findings |
| Liu et al., 2017 | Sweden | 9,430 | Truncal vs selective (including both selective and highly selective) | 1970-2010 | 377,200 | When cases restricted to >5 years after the date of surgery, truncal (but not selective) vagotomy had lower PD risk |
| Svensson et al., 2015 | Denmark | 11,209 | Truncal (including both truncal and selective) vs highly selectiveb | 1977-1995 | 127,211 | Truncal vagotomy had statistically non-significant reduction in PD risk >5 years after surgery, but stronger effect when restricted >20 years |
| Tynnes et al., 2015 | Denmark | 15,079 | Truncal vs selectiveb | 1977-2011 | NR | No significant risk reduction found |

All studies were nationwide cohort studies with data linkage. NR, not reported.

aAlthough 14,883 vagotomy patients were identified, only 11,209 had more than 5 years of postsurgical follow-up.
bDifferent operative coding classification applied to the same data source.
cThe number of cases without vagotomy was not reported, but this data was available to calculate relative risk reduction for the development of PD in patients undergoing different vagotomy procedures.
studies). Together with the potential issue of PD misclassification as a result of the reliance on linkage codes, this means that the statistical power and confidence in the findings are lessened (despite the robust study design). This might help to explain why another study using the same Danish data source—albeit with different coding classification, follow-up duration, and statistical methods—found no significant association between vagotomy and PD risk. Other important methodological considerations include the possibility of reverse causation (although sensitivity analyses exploring longer latencies between vagotomy and PD diagnosis may partially alleviate these concerns), inaccurate coding of surgical procedures, failure to directly account for potential confounders (particularly smoking and anti-inflammatory use), and incomplete data coverage within the registries.

These studies may not have taken into account the fact that retrograde degeneration within the brain occurs following vagotomy, recalibrating the peripheral and central regulation of the gut and other organs. Moreover, the studies may not have factored in that the vagus nerve itself is believed to play an important anti-inflammatory role, acting to dampen splenic immune responses and control intestinal immune activation. Vagotomy has been shown to promote inflammation in experimental studies and this may be another potential confounding factor when assessing whether vagotomy reduces the risk of incident PD.

### Appendectomy and Risk of PD

Other locations have been suggested as potential sites of initiation of PD pathology. In a study of archived surgical specimens from individuals without neurological disease, Gray and colleagues found that α-synuclein immunoreactivity was particularly abundant in the appendix compared to other GI sites. It colocalized there with neural markers and was close to the luminal surface of the appendix, thereby being in the vicinity of any pathogen or triggering event that may originate within the intestine. The lack of a blood–tissue barrier in the appendiceal mucosa might also facilitate contact with the enteric nervous system. Moreover, the rat cecum (analogous to the human appendix) is known to receive substantial vagal efferents. These factors led the authors to speculate that the appendix may be an attractive candidate as an initial focus of environmentally induced α-synuclein aggregation, and therefore surgical removal of this structure (appendectomy) might have a protective effect.

Until recently, there was relatively little epidemiological evidence to support this hypothesis: one retrospective study of 295 PD patients found that appendectomy was associated with a later age of onset (but only in those with disease onset 55 years or older) (Table 2). However, Killinger and colleagues recently provided fresh support for the argument that the normal human appendix does indeed contain pathogenic forms of α-synuclein capable of impacting the risk of developing PD. Using data from the Swedish Patient Registry, the authors reported that PD incidence was 1.60 per 100,000 person-years among individuals with a previous appendectomy (n = 551,647) compared to 1.98 for controls (n = 1,146,353), with the greatest protective effect seen in rural residents. They reported that appendectomy delayed the age of PD onset in the Swedish Patient Registry and confirmed this finding in an independent dataset (Parkinson’s Progression Marker Initiative [PPMI] study). Finally, they showed that the healthy human appendix contained PD-like pathology and that human appendix lysate induced the cleavage and oligomerization of full-length recombinant α-synuclein.

In contrast, other large-scale studies have shown no risk-reducing effect of appendectomy. Marras and colleagues identified individuals aged 35 years or older who had undergone appendectomy over a 20-year period (n = 42,999) using several databases in Ontario, Canada. No protective effect was found on the risk of developing PD when compared with matched individuals who had undergone cholecystectomy or no procedure. In fact, hazard ratios revealed a higher risk of PD in the appendectomy group in the interval shortly after the procedure, which did not persist with increasing length of follow-up. Another Danish population-based study from Svensson and colleagues also found that patients who underwent appendectomy (n = 265,758) had a slightly increased risk of PD when compared with the general population (n = 1,328,790) in those who were followed-up for more than 10 years (hazard ratio, 1.14; 95% confidence interval, 1.03-1.27). Marras et al. suggested that increased contact with the healthcare system might account for the higher risk of PD. This probably does not explain the increased risk seen during a longer follow-up period in the Svensson study, thus raising the possibility that an inflammatory response associated with appendicitis may trigger misfolded α-synuclein in the brain. Recently, another retrospective study found that appendectomy rates were similar in PD compared to other parkinsonian conditions and controls.

### Tonsillectomy and Risk of PD

The appendix is part of the gut-associated lymphoid tissues (GALT), which play an important role in mucosal immunity and protecting the gut from invasion of bacteria. We have already explained that the appendix is directly innervated by the vagus nerve, and so the protective role of appendectomy in some studies could...
be seen as supporting the idea that the “vagal highway” is important in the propagation of PD pathology. An alternative explanation is that GALT act as a key site for immune responses against misfolded α-synuclein (see later discussion on the potential relevance of infection and inflammation in the gut). One way of studying this further is to investigate the tonsils, which are also part of the GALT but lack direct vagal innervation.

In a study from the same group who undertook the recent large appendectomy study, the Swedish Patient Registry was used to show that the incidence of PD among 270,235 individuals with past tonsillectomy (3.32 per 1,000,000 person-years; 35 PD cases) was significantly reduced when compared with 554,727 matched controls (5.04 per 1,000,000 person-years; 110 PD cases). Using PPMI data, they also showed that individuals who underwent tonsillectomy at least 20 years before the onset of PD had an age of onset significantly later than control individuals by an average of 3.43 years. Finally, the authors demonstrated that tonsils obtained from both pediatric and adult subjects contained proteinase K-resistant α-synuclein aggregates, primarily in nonneuronal cells.

The low PD incidence figures in this study probably reflect the relatively young age of the cohort at the time of tonsillectomy (mean age = 18.1 years) who may not all have reached the age of full susceptibility for PD. Having said that, individuals who underwent appendectomy were followed for up to 52 years, which is longer than the only other study investigating the potential protective effect of tonsillectomy on PD risk from Svensson and colleagues (where individuals were followed up to 34 years). In that study, the authors reported that the risk of PD in patients with prior tonsillectomy (n = 195,169) was similar to the general population (n = 975,845).

Interestingly, in variant Creutzfeld Jakob disease (vCJD), a transmissible prion disease, pathology

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study type</th>
<th>Appendectomy</th>
<th>Year of appendectomy</th>
<th>No appendectomy</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killinger et al., 2018</td>
<td>Sweden</td>
<td>Nationwide cohort study with data linkage</td>
<td>551,647</td>
<td>1964-2015</td>
<td>1,146,353</td>
<td>Appendectomy significantly reduced the risk of developing PD by 19.3%</td>
</tr>
<tr>
<td>Mendes et al., 2015</td>
<td>Portugal</td>
<td>Retrospective, observational study</td>
<td>34</td>
<td>NR</td>
<td>261</td>
<td>Association between past appendectomy and age of disease onset for patients with late PD onset only.</td>
</tr>
<tr>
<td>Marras et al., 2016</td>
<td>Canada</td>
<td>Province-wide cohort study with data linkage</td>
<td>42,999</td>
<td>1997-2007</td>
<td>42,995</td>
<td>Higher incidence of PD shortly after appendectomy compared to those having no procedure.</td>
</tr>
<tr>
<td>Svensson et al., 2016</td>
<td>Denmark</td>
<td>Nationwide cohort study with data linkage</td>
<td>265,758</td>
<td>1980-2010</td>
<td>1,328,790</td>
<td>In those with follow-up of more than 10 years, individuals who underwent appendectomy had a slightly increased risk of PD compared to members of the general population cohort.</td>
</tr>
<tr>
<td>Yilmaz et al., 2017</td>
<td>Germany</td>
<td>Retrospective, observation study</td>
<td>69b</td>
<td>NR</td>
<td>1491c</td>
<td>No difference in prevalence of appendectomy in PD patients compared to non-synuclein-related parkinsonism and controls. No difference in PD phenotype in those who had undergone appendectomy.</td>
</tr>
</tbody>
</table>

NR, not reported.

*aMedian age of appendectomy.

*bIn total, 134 patients had a history of appendectomy, of which 69 had PD.

cOf which, 839 had PD, 633 had parkinsonism, and 153 were controls.
initially infects the tonsils and Peyer’s patches in the gut. In fact, tonsillar biopsies were initially proposed as an accurate diagnostic test for vCJD, before other methods were developed. From these lymphoid tissues, prions spread via autonomic nerves to the DMNV, sympathetic ganglia, and the intermediolateral cell column of the spinal cord. This spread of prions is reminiscent of the spreading pattern hypothesized to occur in PD and signals the need for a better understanding of the role of GALT in PD pathogenesis.

Current State of Knowledge

The experimental evidence presented in this review supports the notion that α-synuclein pathology has the ability to spread from certain sites in the GI tract to the brain, but does this adequately explain the origins of PD, or is this an oversimplification?

It is important to recognize that the vagus nerve appears to be a route by which α-synuclein pathology can spread both to and from the brain. This has clinical relevance because it means that accumulation of α-synuclein in peripheral tissues may not necessarily define the site of disease initiation. It is conceivable that the pattern of progression of α-synuclein pathology (caudo-rostral vs rostro-caudal) might vary between patients and depend on the etiology, thus being one of the factors contributing to disease heterogeneity.

Early postmortem studies reported that 33% of controls exhibited Lewy bodies in Auerbach’s plexus with no discernable Lewy body pathology in the brain, although this study predated staining techniques directed against α-synuclein. A consecutive autopsy study in Japan reported isolated Lewy body pathology in the sympathetic ganglia in 5.4% of elderly subjects. Recently, phosphorylated α-synuclein inclusions were detected in pancreatic beta cells in individuals without any Lewy body pathology in the brain (68% and 17% in those with and without type 2 diabetes, respectively). These cases, along with other rare cases of isolated α-synuclein inclusions, are interesting because they show that isolated α-synuclein aggregation in peripheral organs can exist (even if its pathophysiological relevance remains to be determined). The Arizona group, on the other hand, stated in a recent review that they have not seen a single case of isolated Lewy body pathology in the GI tract or any other peripheral region among more than 600 whole-body autopsies. Further research is needed to systematically assess the distribution of pathology in patients with incidental Lewy body disease, as well as to study archived tissue specimens from PD patients who have previously undergone surgical procedures (which has already been ethically sanctioned in some countries without needing to seek additional patient permission). It would also be interesting to study whether colectomies (particularly involving the ascending colon and proximal two-thirds of the transverse colon) were protective against the development of PD.

Even if vagotomy and appendectomy do confer protection against later-life PD, there are likely to be other mechanisms involved in the distribution of α-synuclein pathology in the brain. To begin with, there are many alternative routes by which α-synuclein could spread from the periphery to the brain (such as the olfactory epithelium). In addition, it is likely that only some cases of PD are initiated in peripheral nerve terminals, whereas α-synuclein pathology may arise centrally in the other cases. This would help to explain the previous challenges to the validity of the Braak staging system as the single explanation of PD pathogenesis: one study found that 7% of PD patients had no evidence of α-synuclein pathology in the DMNV.

It is tempting to speculate what factors might trigger PD pathology in the GI tract. Dysbiosis of the gut microbiota has been identified in PD patients. Although it is difficult to separate cause and effect in human studies, it is interesting that signals from gut microbes were found to be capable of promoting α-synuclein-mediated motor deficits and brain pathology in a mouse model of PD, potentially by promoting microglial activation. Together with the observation that α-synuclein expression in the GI tract may be induced by certain infections (thereafter attracting inflammatory cells and contributing to intestinal wall inflammation), it is possible that α-synuclein expression reflects an immune defense mechanism. This fits with the fact that α-synuclein is induced by, but protective of, RNA virus infections (such as West Nile virus). The capability of α-synuclein peptides to trigger helper and cytotoxic T cell responses may also potentiate neurodegeneration (independent of the vagus nerve).

This hypothesis operates on the assumption that the intestinal epithelial barrier is porous enough to allow pathogens to gain access to trigger pathology in enteric neurons. Indeed, it has been shown that α-synuclein aggregation is associated with increased intestinal permeability in some studies. Alternatively, intestinal wall inflammation itself (with or without dysbiosis) may induce α-synuclein aggregation: inflammatory bowel disease was recently reported to be a risk factor for later-life PD. Other mechanisms could also be involved. For example, enteroendocrine cells in the GI tract receive stimuli from the gut lumen and synapse with submucosal enteric nerves and have recently been shown to express α-synuclein that could conceivably misfold and propagate. Further studies are required to uncover how and why α-synuclein expression occurs in GI nerve terminals.
If PD pathology can spread from the peripheral nervous system to the central nervous system, factors that are specific to particular cell types or brain regions probably influence the distribution of pathology. Braak and colleagues were among the first to highlight one potential cause of selective vulnerability in PD: the relationship between axonal characteristics and vulnerability to α-synuclein pathology. In the vagus nerve, it has been repeatedly demonstrated that the long, thin, poorly myelinated fibres of the visceromotor vagal system are far more prone to developing α-synuclein pathology compared to the myelinated fibres relaying viscerosensory inputs or those derived from the nucleus ambiguus. This may also explain the disproportionate amount of pathology seen in other sites such as the long sympathetic neurons in the paravertebral sympathetic ganglia and may relate to the bioenergetic demands of these axons. Physiological neuronal traits (such as slow calcium oscillations) have also been proposed as an explanation for cellular vulnerability to Lewy body pathology.

It has been pointed out elsewhere that Lewy body pathology tends to be confined to particular cellular types (even within the DMNV), which is difficult to explain purely on the basis of spread of α-synuclein pathology between neighbouring cells or via synaptic connectivity. A similarly high degree of neuronal specificity has been observed in transmissible spongiform encephalopathies such as CJD, with selective vulnerability seen in certain neuronal populations (eg, more pathology in parvalbumin-immunoreactive GABAergic interneurons compared to calbindin-immunoreactive GABAergic interneurons). In CJD, the pattern of neuronal damage also differs depending on the prion protein subtype (defined according to a methionine/valine polymorphism at codon 129 and the molecular mass of the protease-resistant component of the misfolded prion protein). Recently, evidence has been put forward to support the view that the conformation of other self-templating proteins may also be crucially important: different strains of α-synuclein and tau induce different patterns of pathology (in terms of seeding potency and cell-type specificity of subsequent protein aggregation) after injection into mouse brains.

When considering the credibility of the bottom-up model of PD pathogenesis, it is crucial to recognize that there remain unanswered questions regarding the extent to which Lewy body topography correlates with neuronal loss. One study from the Netherlands Brain Bank, for instance, found that nigral neuronal loss preceded the local appearance of α-synuclein aggregates in this region in patients with incidental Lewy body disease (Braak stages 1 and 2). Another study found no correlation between nigral cell loss and the burden of Lewy body pathology. As outlined in a review on the neuropathology of α-synuclein propagation, there are also brain regions (such as the amygdala, DMNV, locus coeruleus, and neocortex) where there is limited neuronal loss in at least a proportion of patients at end-stage, despite a dense burden of Lewy body pathology. Therefore, the precise role of α-synuclein in PD-related neurodegeneration and the factors that influence selective vulnerability in different cell types warrant further scrutiny.

In summary, this review focused on the potential of α-synuclein pathology to spread to the brain via the vagus nerve. The extent to which this is a key causative step in PD remains to be proven. If spread of α-synuclein from the peripheral to central nervous system does occur, it is likely to be only one of several routes (highways) or mechanisms involved in initiating or perpetuating the neurodegenerative process, and not even the only link between the GI tract and the central nervous system. For instance, recent evidence has highlighted that tonsillectomy may protect against the development of PD, which raises the possibility that GALT may have an important role to play in the initiation of PD pathology. Other novel gut-brain connections, such as the link between sensory neurons in the upper gut and striatal dopamine release via the right vagus nerve, are also emerging. Future research will seek to provide additional evidence to support the relationship between the gut and brain health in patients with (or at risk of) PD, which may open up new avenues for therapeutic intervention.

Acknowledgments: Dr. Breen is supported by a Rowling Scholarship from the Anne Rowling Regenerative Neurology Clinic (University of Edinburgh) and has been recipient of an Edmond J. Safra Fellowship in Movement Disorders via the Michael J. Fox Foundation. Prof. Halliday holds a National Health and Medical Research Council Senior Principal Research Fellow.

References


