How Does Parkinson’s Disease Begin? Perspectives on Neuroanatomical Pathways, Prions, and Histology

Per Borghammer, MD, PhD, DMSc

Department of Nuclear Medicine & PET Centre, Aarhus University Hospital, Aarhus C, Denmark

ABSTRACT: Parkinson’s disease (PD) is a multisystem disorder involving peripheral nervous system. Misfolding and aggregation of α-synuclein is central to the pathogenesis of PD, and it has been postulated that the disease may originate in olfactory and gastrointestinal nerve terminals. The prion-like behavior of α-synuclein has been convincingly demonstrated in vitro and in animal models of PD. Lewy-type pathology have been detected in peripheral organs many years prior to PD diagnosis, and 2 independent studies have now suggested that truncal vagotomy may be protective against the disorder. Other lines of evidence are difficult to reconcile with a peripheral onset of PD, most importantly the relative scarcity of post mortem cases with isolated gastrointestinal α-synuclein pathology without concomitant CNS pathology. This Scientific Perspectives article revisits some important topics with implications for the dual-hit hypothesis. An account of the neuroanatomical pathways necessary for stereotypical α-synuclein spreading is presented. Parallels to the existing knowledge on true prion disorders, including Creutzfeld-Jakob disease, are examined. Finally, the vagotomy studies and the somewhat inconsistent findings in the growing literature on peripheral α-synuclein pathology are discussed. It is concluded that the dual-hit hypothesis remains a potential explanation for PD pathogenesis, but several issues need to be resolved before more firm conclusions can be drawn. © 2017 International Parkinson and Movement Disorder Society

Key Words: Parkinson’s disease; α-synuclein; Lewy; dual-hit hypothesis; prion

Parkinson’s disease (PD) is a multisystem disorder that involves the central and peripheral nervous systems. Recent decades have witnessed a considerable expansion in our knowledge of the pathogenesis and molecular characteristics of PD. The neuronal inclusion bodies originally identified by Friedrich Lewy in 1912 contain pathological aggregates of the normally soluble small protein α-synuclein (α-syn). The spatial distribution of Lewy neurites and bodies in the brain of PD patients is not random, but generally compatible with a staging scheme proposed in 2003 postulating that inclusions initially appear in the olfactory bulb and dorsal motor nucleus of the vagus (DMV) in the lower brain stem. The pathology then seems to ascend in a predictable fashion with subsequent involvement of monoaminergic pontine nuclei and the dopaminergic neurons of the substantia nigra. The credibility of this idea has gained further support because α-syn exhibits prion-like properties, including the propensity to misfold and formation of aggregates, which display cell-to-cell transmission.

The “dual-hit hypothesis” extended this explanatory framework by postulating that initial formation of α-syn aggregates occurs outside the brain, that is, in the terminal end fields of neurons residing in the olfactory bulb and the preganglionic parasympathetic neurons of the DMV. This concept presents a potential explanation as to why the olfactory bulb and DMV show early, severe involvement in most cases of PD, but is also controversial because it implies that PD could in part be caused by exterior insults such as toxins or microorganisms. Also, not all lines of evidence are supportive of the dual-hit hypothesis, which has led to alternative theories about the origin of PD.
In this Scientific Perspectives article, several important topics with implications for the dual-hit hypothesis will be examined. First, the stereotypical spreading pattern presupposes the existence of specific neuronal interconnections. An account of these neuroanatomical pathways is provided. Second, centripetal spreading of peripherally administered α-syn aggregates in transgenic rodent models of PD has been demonstrated. Such seeding experiments have been performed for several decades in models of true prion diseases such as bovine spongiform encephalopathy and scrapie. The similarities between these prion models and the α-syn PD models are discussed. Third, a number of studies have investigated the presence and distribution of pathological α-syn assemblies in the peripheral organs of PD patients. Recently, we and others have reported that Lewy-type pathology is detectable in the gastrointestinal tract up to 20 years prior to PD diagnosis. However, the literature also shows inconsistencies and, in addition, some important findings go against the dual-hit hypothesis. Fourth, in 2015, we reported that truncal vagotomy substantially reduces the risk of PD. The implications of this finding are discussed.

**Neuro-Anatomical Pathways Subserving α-Syn Propagation**

A number of neuro-anatomical tracer studies have demonstrated the existence of relevant neuronal interconnections (summarized in Figure 1). Most studies employed classical retrograde and anterograde staining techniques such as horseradish peroxidase, fluorogold, and phaseolus vulgaris leucoagglutinin in rodents, cats, and monkeys. More advanced methods have also been used, including bidirectional tracers and barcode messenger RNA (mRNA) sequencing techniques.

Several important observations arise from this literature. First, the most relevant mono-synaptic interconnections necessary for the hypothesized stereotypical α-syn spreading pattern have been demonstrated. The DMV is connected to the raphe nuclei and locus coeruleus (LC), which are in turn connected to the substantia nigra. Importantly, no direct mono-synaptic pathways have been found between the DMV and the nigra, which could conceivably introduce a time lag for the α-syn propagation from the lower brain stem to the mesencephalon.

Second, the spinal cord including the preganglionic sympathetic neurons of the intermediolateral cell column (IML) is directly connected to the LC and neighboring noradrenergic A5 nucleus as well as to the caudal raphe complex and magnocellular nucleus of the reticular formation (not shown in Fig 1). A small fraction of PD patients (<10%) do not show α-syn pathology in the DMV postmortem, but these cases most often exhibit involvement of the LC and raphe nuclei. If pathological α-syn species truly reach the brain stem via autonomic nerves, these aberrant PD cases could therefore be explained by a predominantly sympathetic involvement and subsequent IML-to-LC spreading, which would bypass the DMV. However, autopsy cases with isolated α-syn pathology in the spinal cord but not in the CNS are rare, which argues against this spreading route.

Third, the nigra and especially the LC are directly connected to the olfactory bulb. Indeed, a recent study using high throughput mapping of barcoded mRNA demonstrated that 23% of LC neurons directly innervate the olfactory bulb in mice. At the initial formulation of the Braak staging scheme, the importance of early olfactory bulb pathology was questioned because few incursions into related olfactory regions were seen. However, the direct pathways from the LC and nigra to the bulb provide yet another route of entry from a Braak stage 1 structure to the pons and mesencephalon—a pathway that also bypasses the DMV.

In summary, known neuro-anatomical pathways are compatible with a peripheral-to-central spreading pattern and the interconnections also provide potential explanations why not all PD cases strictly follow the original Braak staging system. On the other hand, the existence of these pathways does not per se prove that PD originates in peripheral organs, only that it is a theoretical possibility.

**Prions and PD**

The prion concept in PD and Alzheimer’s disease has been the subject of several recent reviews to which the reader is referred for a full account on this topic. The normally soluble protein α-syn is predominantly found in nerve terminals and may be involved in neuronal vesicle transport. Interestingly, recent studies have shown that native α-syn may be a neuron-specific inhibitor preventing access of neuroinvasive viruses to the central nervous system perhaps by inhibiting viral exocytosis pathways. The α-syn has the propensity for spontaneous misfolding and displays prion-like properties in vitro, including cell-to-cell propagation. Both retro- and anterograde axonal transport of α-syn fibrils have been demonstrated in the vagal nerve, and pathological aggregates were detected in the DMV 1 week after injection of α-syn fibrils in the duodenum of rats. Recently, it was shown that a single intra-peritoneal injection of α-syn fibrils in A53T transgenic mice led to marked neurological symptoms after an incubation period of ~7 months. Severe widespread α-syn pathology was seen in the spinal cord, brain stem, and cerebrum.
Thus, there is little doubt about the prion-like properties of α-syn in animal models, but no formal evidence have demonstrated that similar prion-like spreading occurs in human PD patients. Interestingly, a recent report suggested that iatrogenic transmissible Alzheimer pathology may have developed decades after treatment with cadaveric pituitary-derived growth hormone in adolescence.42

Some observations and findings in true prion disorders such as Creutzfeldt-Jakob disease (CJD) may have relevance for PD. In the prion field, seeding experiments in animal models have been performed for decades, and Figure 2 summarizes the main findings.

After oral infection with bovine spongiform encephalopathy–associated or scrapie-associated prions in cattle, sheep, and hamsters, the initial prion aggregates are seen in the gut-associated lymphoid tissue of the tonsils and Peyer’s patches.43-47 The subsequent spreading of prions through nervous tissues shows similar spatial and temporal characteristics in these animal models. Often, the first prion aggregates are seen in the coeliac-mesenteric ganglia (CMG) followed by involvement of the DMV and IML (Figure 2A). From these initial entry points, the pathology spreads throughout the CNS, but the involvement of the telencephalon is a relatively late phenomenon. It should also be noted that prion aggregates are seen in efferent pathways before afferent, that is, the CMG and IML are affected before the dorsal root ganglia, and the DMV before the nodose ganglion.43,44 A similar predilection for retrograde transport through efferent fibers may also be the case in PD, suggested by the much more severe involvement of the DMV compared to the sensory vagal nuclei3 and also by the demonstration that virtually all vagal efferents to the gut express α-syn, whereas vagal afferents in the myenteric plexus and GI smooth muscle do not.48 Thus, the initial spreading of prions through the autonomic nervous system in these animal models is highly similar to the hypothesized route of α-syn propagation in PD.

The most common human prion disease is CJD, in which ~1% of cases represent the acquired variant CJD (vCJD); 85% to 90% are sporadic (sCJD), and approximately 10% are familial.49 Several postmortem studies have revealed striking differences between acquired and sporadic/familial CJD. In vCJD autopsies, prions were detected in the lympho-reticular system of the tonsils, spleen, and lymph nodes,50 and the appendix also showed consistent involvement—in 1 vCJD case, 8 months prior to disease onset.51 Prions have also been detected in the coeliac and stellate ganglia and were found to colocalize with sympathetic postganglionic neurons.52 In contrast, such peripheral prion pathology is never seen in sCJD, but is confined to the CNS.

**FIG. 1.** Summary of relevant neuro-anatomical pathways necessary for α-syn propagation. Braak stages are color coded. Pre- and postganglionic cell groups of the sympathetic nervous system are shown in gray. Numbers in brackets designate references.12-24 CeA, central nucleus of amygdala; CG/MG, celiac & superior mesenteric ganglia; DMV, dorsal motor nucleus of vagus; IML, intermediolateral cell column; LC/A5, locus coeruleus and noradrenergic A5 nucleus; OB, olfactory bulb; PVN, paraventricular nucleus; RN, raphe nuclei; SG, stellate ganglion; SN, substantia nigra. [Color figure can be viewed at wileyonlinelibrary.com]
These findings in vCJD support the experimental prion animal literature and suggest that initial disease propagation in some acquired prion disorders occurs via the autonomic nervous system. In contrast, the initial misfolding event in the much more frequent sporadic/familial prion disorders probably arises through a spontaneous stochastic event within the CNS.\(^5\) In PD, it was originally suggested that \(\alpha\)-syn pathology may preferentially originate in the terminals of neurons with long, nonmyelinated, hyper-branched axons.\(^5,6\) This proposition would partly explain why autonomic nerves are so prone to formation of Lewy pathology, as these axons are among the longest and most hyper-branched in the body. One possibility is that the initiation point in a given PD case may be a stochastic event—similarly to sCJD. In other words, the pathology in most PD patients may originate in olfactory, gastrointestinal, and/or cardiac nerve endings because these are statistically the most likely sites of stochastic \(\alpha\)-syn misfolding. In addition, the propensity to misfold could be further enhanced by the close proximity of these nerve endings to exogenous toxins and microorganisms. Whether such exogenous factors are of major importance in the pathogenesis of PD is at present unknown, but pesticides have been linked to increased risk of PD,\(^54\) and gastric lavage with rotenone was shown to induce \(\alpha\)-syn aggregation and secondary spreading to the CNS in a mouse model.\(^55\) Perturbations in the gut microbiota might also predispose toward enhanced \(\alpha\)-syn misfolding and aggregation.\(^56,57\) Finally, the purported protective effect of tobacco use\(^58\) could be related to a direct anti-aggregation effect on the olfactory and gastrointestinal nerve terminals.

### Pathological \(\alpha\)-Syn in Peripheral Organs

In diagnosed PD patients, pathological \(\alpha\)-syn aggregations have been detected in various peripheral tissues, including the nervous plexuses of the gastrointestinal tract,\(^59,63\) heart,\(^64\) salivary glands,\(^63,65,66\) and skin.\(^67,68\) However, to assess whether pathological \(\alpha\)-syn appears during the preclinical phase, studies of prodromal cases, archived tissues, and autopsy material from neurologically intact individuals with or without incidental Lewy body disease (ILBD) are necessary.

Several autopsy studies have, in addition to PD patients, included a number of ILBD cases and reported pathological \(\alpha\)-syn aggregates in peripheral organs, including gastrointestinal nerve plexuses and sympathetic ganglia.\(^2,3,30,61,63,69,70\) However, the prevalence of peripheral \(\alpha\)-syn pathology is generally lower in ILBD than in diagnosed PD and DLB cases.

Studies of patients with idiopathic rapid eye movement sleep behavior disorder reported that 56% of cases displayed phosphorylated \(\alpha\)-syn in dermal fibres, and 8 of 9 cases were positive in the salivary glands.\(^71,72\) A few studies examined archived tissue...
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specimens removed from PD patients years prior to diagnosis. In one study, 9% of PD cases (3/33) were positive for phosphorylated α-syn in the gastrointestinal tract, whereas another reported 67% (2/3) positive cases.73,74 No positive controls were reported in these studies. We found that 56% (22/39) of PD cases harbored phosphorylated α-syn aggregates in the gut up to 20 years prior to diagnosis, but 26% (23/90) of matched control tissues were also positive.10

An important criticism of the peripheral onset hypothesis in PD stems from the relative lack of cases with isolated peripheral α-syn pathology in the absence of CNS involvement. A total of 466 whole-body autopsies from the Arizona study of Aging and Neurodegenerative Disorders suggest that the olfactory bulb is the most common site of isolated α-syn pathology.75 However, this group of researchers has not encountered a single case in which pathological α-syn was present in a peripheral body region but not in the CNS.66 In contrast, Japanese studies have reported a number of cases with isolated α-syn pathology in the myenteric plexus of the esophagus and small intestine, the paraspinal sympathetic ganglia, adrenal glands, and also some cases with pathology restricted to the ganglia and thoracic IML.30,76-78 It should be noted that 1 of these studies was published prior to the era of α-syn immunohistochemistry, and the findings should be interpreted with caution. Put together, these data are compatible with the olfactory bulb being a probable entry point. At face value, the scarcity of cases with isolated gastrointestinal α-syn pathology could be considered a coup de grâce for the “gut part” of the dual-hit hypothesis. Still, several factors need to be taken into account.

First, in a brain-stem nucleus such as the DMV, thousands of neurons are situated closely together, which maximizes the probability of detecting pathology. In contrast, the terminal fields of the DMV neurons are widely distributed across the thoracic and most abdominal organs. If the terminal axonal branches are heterogeneously affected by α-syn pathology, it follows that the false negative rate could be considerably higher for detection of peripheral pathology, whereas central lesions will be much easier to find because the pathology is siphoned toward the same localized, compact nuclei.

Second, the time window from terminal α-syn misfolding to the appearance of aggregates in the soma located in the CNS could in theory be relatively short (weeks), as suggested by animal evidence.40 Also, sparse and highly localized terminal pathology may be sufficient to initiate retrograde transport of α-syn aggregates. Detecting such limited and localized peripheral pathology in just the right time window before central pathology appears may be like finding the proverbial needle in the hay stack. This concept is supported by observations from the prion literature. In cattle, which were orally challenged with bovine spongiform encephalopathy, prions were detected in the CMG, IML, and DMV, whereas the animals were negative in the myenteric or submucosal plexuses.46 Thus, prion pathology, which with certainty have entered through the gastrointestinal tract and subsequently spread to the CNS, can remain below detection threshold in the periphery while being detectable in the brain. Interestingly, a similar finding was reported in a single autopsy case of kuru, a prion disorder transmitted via endocannibalism among the native population on Papua New Guinea. Here, spongiosis and prions were seen in the cortex, basal ganglia, thalamus, and brain stem. Limited pathology was seen in the spinal cord and roots, and none was found in peripheral tissues, including the ileum and spleen.79

Third, the most commonly used immunohistochemical methods are optimized toward detection of macroaggregates, that is, inclusion bodies and neurites. However, the formation of mature aggregates is preceded by oligomeric and proto-fibril species.80 Several studies have shown that α-syn oligomers disseminate more efficiently than higher molecular weight assemblies,81-83 and retrograde vagus-mediated transport of α-syn oligomers has been demonstrated in an in vivo rat model.40 Therefore, it cannot be ruled out that retrograde axonal transmission of α-syn oligomers and proto-fibrils may precede the formation of mature α-syn aggregates in the periphery. Current immunohistochemical techniques may lack the sensitivity to detect such early aggregates. Interestingly, a recent study used a proximity ligation assay to detect α-syn oligomer species in brain tissue and was able to detect significantly more pale bodies and extra-somal Lewy bodies than standard immunohistochemistry, suggesting greater sensitivity to earlier lesions.84 Another technique termed real-time quaking-induced conversion exploits the ability of prion protein to self-aggregate and showed a diagnostic accuracy of >97% for diagnosing sCJD patients using nasal brushings.85 This assay has now been adapted for α-syn detection and has shown high diagnostic accuracy for diagnosing PD in CSF samples.86 Such techniques could conceivably also improve detection rates of α-syn pathology in peripheral tissues.

Fourth, it is now recognized that current immunohistochemical methods for detecting α-syn pathology in peripheral organs suffer from lack of standardization and difficulties of interpretation. This is underscored by published rates of positive colonic staining in neurologically intact individuals, which varies from 0%59,87 to nearly 100%88,89 Also, skin biopsies from PD patients were positive in 100% of cases in one study, but 0% in another.63,67 Consequently, multicenter studies are now being carried out to optimize
staining protocols and homogenize interpretation. An important goal will be to define robust criteria for what constitutes pathological staining in peripheral organs, but this task is made difficult by the lack of definite negative controls. It is known that 10% to 30% of aged subjects without clinical parkinsonism or dementia display Lewy pathology in the brain post-mortem. Also, the prevalence of incidental Alzheimer-type amyloid pathology increases from 15% to 44% in the 60-90-year range in cognitively intact individuals. In other words, it cannot automatically be expected that healthy aged individuals without ILBD do not harbor pathological α-syn aggregates in peripheral organs. For this reason, staining patterns seen in aged non-ILBD subjects cannot automatically be designated as physiological or nonspecific. Further validation studies may require inclusion of tissue from very young subjects, where pathological α-syn aggregates are probably less frequent. To my knowledge, this is currently not an active field of investigation.

In summary, the relative lack of postmortem cases with isolated peripheral α-syn pathology for the moment weakens the case for a gastrointestinal onset in PD. However, several issues need to be resolved before more firm conclusions can be drawn.

### Protective Effect of Vagotomy

If the vagal nerve constitutes a major highway for centripetal spreading of α-syn pathology, it follows that vagotomy could be protective against PD. Prior to the *Helicobacter pylori* era, vagotomy was a commonly used treatment for peptic ulcer. Three principal types of vagotomy were employed: full truncal vagotomy; selective vagotomy where only vagal branches to the stomach were cut, and the most refined super-selective vagotomy, where only the corpus and fundus were denervated. Only truncal vagotomy would be expected to significantly prevent retrograde propagation of α-syn aggregates.

Observations from animal models support that sectioning parts of the autonomic nervous system delays the neuroinvasion of peripherally seeded protein aggregates. In a hamster scrapie model, chemical or immunological sympathectomy significantly delayed (but did not prevent) the spreading of scrapie-type prions to the CNS after intraperitoneal injection. Similar findings were seen in the rotenone mouse model of PD, although concerns have been raised about the reproducibility of this model. When the stomach of mice is exposed to the mitochondrial poison rotenone, α-syn aggregation and subsequent spreading to the brain stem via the vagus has been demonstrated. However, both partial sympathectomy and hemivagotomy significantly delayed the development of motor symptoms in the animals. Also, partial sympathectomy delayed the appearance and diminished the amount of pathological α-syn in the IML, and hemivagotomy prevented accumulation of α-syn in the ipsilateral DMV. Intriguingly, hemivagotomy also seemed to prevent cell death in the ipsilateral SNC.

In 2015, we published the first epidemiological study to test whether vagotomy modifies the risk of PD. Cohorts of patients, who had undergone vagotomy during 1977-1995 were constructed and compared to matched controls. Of note, the statistical power of our study may have been blunted because truncal and selective vagotomy patients were binned into 1 group because of concerns of registry code validity. Only super-selective vagotomy patients could be isolated and analyzed separately. After >20 years of follow-up, the truncal/selective vagotomy cohort showed a significantly decreased risk of PD compared to the background population (hazard ratio [HR] = 0.53; 95% confidence interval [95% CI] 0.28-0.99). A nonsignificantly decreased risk of PD was also seen when comparing the truncal/selective group directly to the super-selective group (HR = 0.58; 95% CI 0.28-1.20).

This finding has now been reproduced by Swedish researchers. Importantly, here the truncal vagotomy patients were uniquely identifiable, and the selective and super-selective cases were binned into 1 group. The truncal vagotomy group exhibited a decreased risk of PD after >5 years of follow-up when compared with the background population (HR = 0.59; 95% CI 0.37-0.93), and also when compared with the selective/super-selective group (HR = 0.54; 95% CI 0.32-0.91). Thus, the risk-modifying effect of truncal vagotomy has been detected in 2 independent datasets.

Of note, the Danish vagotomy data set was independently analyzed by a Norwegian research group. The study was published as a brief letter and contains sparse details on the statistical methodology making a critical evaluation difficult. The Norwegian group included all 15,079 vagotomy subjects operated during 1977-2011. We identified nearly the same number, that is, 14,893 subjects operated during the golden era of vagotomy (1977-1995) prior to the *H. pylori* treatments. The follow-up period was 1 year longer in our study. The Norwegian group analyzed truncal and selective vagotomies in 2 separate groups, which was not completely valid because surgical codes of truncal and selective vagotomy are known to be unreliable in the Danish registers. However, both operations require pyloroplasty, so a combined truncal/selective group can be unequivocally identified based on the concomitant pyloroplasty code, which was the strategy we employed. Tysnes and colleagues focused only on significance testing and found no significant
protective effect of vagotomy. They did not report important estimates of relative risk with confidence intervals in vagotomy patients stratified on follow-up time (<10 years and 10-20 years). In contrast to our study, they also did not impose a minimum follow-up criterion on the data, but accepted PD cases in the vagotomy cohorts even if patients were diagnosed immediately after vagotomy. The prodromal phase in PD is thought to span 5 to 20 years, with early involvement of the brain stem. Thus, if a patient develops PD within a few years after vagotomy, the pathology was conceivably already in the brain stem at the time of vagotomy. By not imposing a minimum required follow-up time from vagotomy to PD diagnosis, the protective effect of vagotomy will likely be more difficult to detect. This concept is underscored by the Swedish findings. When using the entire follow-up period (0-30 years) a smaller protective trend was observed (HR = 0.78; 95% CI 0.55-1.09), but when restricting the follow-up period to >5 years a larger effect was seen (HR = 0.59; 95% CI 0.37-0.93). In summary, the analysis of Tysnes and colleagues 103 differed from ours in a number of important ways, and the findings in the 2 studies cannot be directly compared.

A number of epidemiological studies have reported an increased risk of PD risk following various types of infections and inflammation, including hepatitis C, herpes viruses, influenza, and H. pylori.105-109 Interestingly, both vagotomy studies reported an increased PD risk (HR = ~1.1-1.2) among the selective/super-selective vagotomy patients compared to the background population. Although these findings were not statistically significant, they are nevertheless supported by the observation in a Danish register study that H. pylori treatment is associated with a 45% increased risk of PD.107

One intriguing possibility is that gastrointestinal inflammation caused by infections or ulcers could predispose to α-syn aggregation. Recently, we and another research group showed that appendectomy carries an increased risk of subsequent PD.110,111 Again, a possible interpretation is that the inflammatory state (ie, appendicitis) preceding the appendectomy increases the risk of initiating the α-syn aggregation cascade. At the moment, this hypothesized association between gut inflammation/infection and α-syn aggregation remains speculative, but the novel findings that native α-syn may inhibit the access of neuro-invasive viruses to the CNS could be involved.33,34 Such infection/α-syn aggregation interactions could potentially be studied in the novel transgenic rodent models of PD. Also, more epidemiological studies are needed to elucidate if respiratory, gastrointestinal, and urogenital infections in general may predispose to PD.

In summary, the vagotomy findings support the dual-hit hypothesis, but alternative explanations cannot be ruled out. For instance, the vagus is critically involved in a cholinergic anti-inflammatory pathway with the ability to suppress both local and systemic inflammation.112 It is at present largely unknown how truncal vagotomy affects inflammatory responses in humans, and especially how such modifications of inflammatory mechanisms might affect cellular capabilities to deal with α-syn aggregates.

**Conclusions—Where Does PD Begin?**

At the time of its conception, the “dual-hit” hypothesis6,7,113 was controversial and to a certain extent it still is. Nevertheless, it cannot be denied that a range of observations and findings in PD is supportive of this hypothesis. Hyposmia and constipation are frequent nonmotor symptoms appearing years or decades prior to PD diagnosis. Lewy-type pathology in peripheral tissues has been detected up to 20 years prior to diagnosis. Two independent studies reported that the risk of PD may be substantially decreased following truncal vagotomy. Finally, accumulating evidence from animal studies clearly demonstrates the prion-like properties of α-syn, including centripetal spreading following peripheral administration of pathological aggregates. Of note, the spreading pattern is similar to that seen in animal models of true prion disorders such as scrapie and also similar to autopsy findings in patients with acquired CJD.

Other lines of evidence are difficult to reconcile with a peripheral onset of PD, most notably the relative lack of autopsy cases with isolated peripheral α-syn pathology in the absence of CNS involvement. However, the field of α-syn staining of peripheral tissues is still immature. More studies are needed to refine staining methods and define robust criteria on how to interpret staining patterns in the gastrointestinal tract and other tissues. At the moment, we have insufficient knowledge about what constitutes a pathological α-syn aggregate in peripheral tissues. Also, it is unclear whether α-syn oligomers and proto-fibrils formed in peripheral tissues are sufficient for retrograde transport to the brain stem or spinal cord, where peripheral pathology is still sparse and difficult to detect. It may be necessary to implement methods for detecting and quantifying oligomeric and proto-fibrillar α-syn species in peripheral tissues to answer some of these questions. In addition, a “brain first” or a “nose first” hypothesis of PD etiopathogenesis also needs to account for why truncal vagotomy seems to be protective against the disease.

Multiple system atrophy and limbic-predominant DLB are also α-synucleinoathies, but with different...
distributions of the pathological α-syn aggregates in comparison to PD. It appears more difficult to argue that these disorders originate in the gut, although an olfactory bulb entry hypothesis has been suggested for DLB. In any case, CJD constitutes an interesting parallel. Many fundamental aspects of sporadic and variant CJD are similar, but one is an acquired prion disease travelling through the autonomic nervous system—the other arises much later in life probably as a result of an “unfortunate” stochastic event within the CNS. Perhaps the α-synucleinoathies will eventually be categorized into similarly discrete categories with distinct initiation points of pathological protein aggregation.

Finally, if α-syn aggregation is initiated in peripheral nerve terminals of the olfactory and gastrointestinal lining, this presents some interesting prospects for therapeutic interventions. Even small amounts of ingested or inhaled agents would reach these target zones in high concentrations, and the ability to cross the blood–brain barrier would not necessarily be a requirement.

References


