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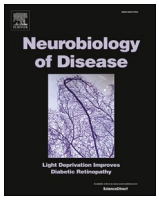

Review

Body-first Parkinson's disease and variant Creutzfeldt–Jakob disease – similar or different?

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ABSTRACT

In several neurodegenerative disorders, proteins that typically exhibit an α-helical structure misfold into an amyloid conformation rich in β-sheet content. Through a self-templating mechanism, these amyloids are able to induce additional protein misfolding, facilitating their propagation throughout the central nervous system. This disease mechanism was originally identified for the prion protein (PrP), which misfolds into PrP^{Sc} in a number of disorders, including variant Creutzfeldt–Jakob disease (vCJD) and bovine spongiform encephalopathy (BSE). More recently, the prion mechanism of disease was expanded to include other proteins that rely on this self-templating mechanism to cause progressive degeneration, including α-synuclein misfolding in Parkinson's disease (PD). Several studies now suggest that PD patients can be subcategorized based on where in the body misfolded α-synuclein originates, either the brain or the gut, similar to patients developing sporadic CJD or vCJD. In this review, we discuss the human and animal model data indicating that α-synuclein and PrP^{Sc} misfolding originates in the gut in body-first PD and vCJD, and summarize the data identifying the role of the autonomic nervous system in the gut-brain axis of both diseases.

1. Introduction

A growing body of research in the neurodegenerative disease field points to the contribution of protein misfolding and aggregation as the underlying cause of the progressive degeneration observed in patients (Prusiner, 2017; Goedert, 2015; Jucker and Walker, 2018). In these proteinopathies, an intrinsically disordered protein misfolds to adopt an amyloid conformation that is rich in β-sheet content. As a result of this misfolding, the amino acid side chains project outward, enabling the formation of hydrogen bonds between the carbon backbone of individual amino acids present in the templating region of the protein. These hydrogen bonds contribute to the high stability of amyloid fibrils that are resistant to denaturation by enzymes and harsh chemicals (Prusiner, 1982; Gordon, 1946). Moreover, the large number of intermolecular bonds facilitate the self-templating process, resulting in additional protein misfolding (Fig. 1). This mechanism, known as the prion mechanism of disease, was first described for the conformational shift observed from the cellular prion protein (PrP^{C}) into the disease-causing scrapie conformation (PrP^{Sc}) (Prusiner, 1982), which is responsible for a variety of fatal neurodegenerative disorders including Creutzfeldt–Jakob disease (CJD) in humans, bovine spongiform encephalopathy (BSE) in cattle, chronic wasting disease (CWD) in cervids, and scrapie in sheep and goats. As a disease mechanism, the prion hypothesis was initially criticized because it was unclear how an individual protein could give rise to a variety of neurodegenerative disorders in the absence of a nucleic acid. Ultimately, however, the strain hypothesis emerged, stating that the shape, or conformation, that the misfolded PrP^{Sc} adopts determines the disease an individual will develop (reviewed in (Bartz, 2017; Bartz, 2021)). These differences in conformation result in varied biochemical properties for each PrP^{Sc} strain, which manifest as varied disease kinetics, fibril stability, neuropathological lesions, and disease presentation (Bartz, 2017; Bessen and Marsh, 1992a; Bessen and Marsh, 1992b; Peretz et al., 2001; Thackray et al., 2007; Ayers et al., 2011; Fraser and Dickinson, 1967; Fraser and Dickinson, 1968). Since its initial proposal in 1982, the prion disease mechanism has subsequently been observed in several additional proteins including α-synuclein, tau, β-amyloid, TDP-43, and SOD1 (reviewed in (Holec and Woerman, 2021; Vaquer-Alicea et al., 2021; Lau et al., 2021; Ayers and Borchelt, 2021)).

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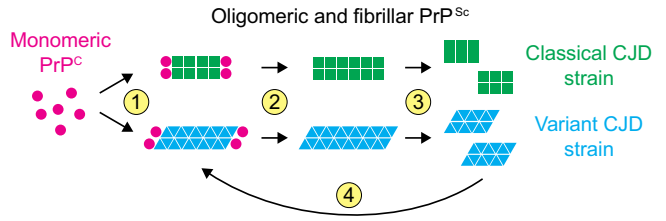

Fig. 1. Sporadic CJD and variant CJD prions replicate as distinct strains. (1) Monomeric PrP^{C} (magenta circles) is recruited to oligomeric or fibrillar assemblies of PrP^{Sc} (green squares and blue triangles). (2) Upon binding to PrP^{Sc}, PrP^{C} undergoes a conformational conversion and adopts the same conformation as the recruiting PrP^{Sc} strain, which results in the formation of new PrP^{Sc} molecules and growth of existing PrP^{Sc} assemblies. (3) Growing fibrils of PrP^{Sc} fragment and create smaller fibrils with additional free ends. (4) In a catalytic cascade, these newly created fibril ends recruit and convert more PrP^{C} into PrP^{Sc}. Each prion strain, e.g., sCJD and vCJD, has a specific conformation that determines its properties, including stability, pathogenicity, and the clinical disease it induces.

Moreover, distinct strains of these amyloidogenic proteins also give rise to a variety of diseases. For example, α-synuclein misfolding into different conformations is responsible for both Parkinson's disease (PD) and multiple system atrophy (MSA) (Spillantini et al., 1997; Spillantini et al., 1998). Adding to the complexity of these diseases, the clinical manifestation is impacted by where in the body the misfolding process initially occurs. Recent findings suggest that PD patients can be subcategorized into either brain-first or body-first PD, which is thought to be determined by where α-synuclein misfolding originates (Horsager et al., 2020). In this review, we will focus on the similarities and differences between PD and CJD, with a particular emphasis on body-first PD and variant CJD (vCJD).

2. Parkinson's disease – a disorder of two origins?

PD was first described by James Parkinson in 1817, identifying a shaking palsy in patients presenting with a resting tremor, limb rigidity, and a slow, shuffling gait (Parkinson, 1817). Almost 100 years later, in 1912, Fritz Heinrich Lewy identified the presence of eosinophilic inclusions in specific brain nuclei in PD patient samples (Forster and Lewy, 1912), which became known as Lewy bodies (LBs). The protein makeup of LBs was not understood until 1997, when Maria Grazia Spillantini and her coworkers determined that aggregated α-synuclein, a cytosolic protein of 140 amino acids encoded by the *SNCA* gene, is a major component of these neuronal inclusions (Spillantini et al., 1997). Following this foundational discovery, analysis of post-mortem tissue from PD patients by Heiko Braak and colleagues aimed to identify patterns of α-synuclein deposition in the brain (Braak et al., 2003a). These studies resulted in the dual-hit hypothesis, arguing that α-synuclein pathology spreads from the nerve terminals of the enteric nervous system (ENS) into the dorsal motor nucleus of the vagus (DMV). At the same time, pathology develops in the olfactory bulb, and both the DMV and the olfactory bulb then serve as entry points into the central nervous system (CNS). From these two brain regions, pathology spreads first to the locus coeruleus and substantia nigra, and then progresses to higher order cortical regions. The idea that *body-first PD* originates in the ENS is consistent with the observation that patients frequently experience constipation and delayed gastric emptying as early non-motor symptoms (reviewed in (Liddle, 2018; Borghammer, 2018; Poirier et al., 2016; Kujawska and Jodynis-Liebert, 2018)), as well as the recent finding that gastrointestinal infections are associated with an increased risk of developing PD (Nerius et al., 2020). Moreover, epidemiological analyses of data from patients treated with a vagotomy to prevent peptic ulcers found that patients receiving a complete truncal vagotomy showed a reduced risk of developing PD if the vagotomy was performed more than five years before disease onset (Svensson et al., 2015; Liu et al., 2017). In contrast, patients who received a superselective vagotomy (targeting nerves to the fundus and body of the stomach only) had a similar risk of disease as the general public (Svensson et al., 2015).

While there are substantial data supporting the hypothesis that PD originates in the ENS, there is also a subpopulation of PD patients who do not develop LBs in the DMV, suggesting that these patients may instead develop *brain-first PD (*Parkkinen et al., *2008)*. In 2008, a review of α-synuclein immunostaining in 1,720 autopsy samples by Parkkinen *et al.* found that 17% of the 226 synucleinopathy patients in the cohort lacked LB neuropathology in the DMV. These findings are consistent with reports of limbic- and amygdala-predominant LBs in PD patients with little to no involvement of the DMV or the rest of the pons and medulla (Raunio et al., 2019; Kosaka et al., 1984; Beach et al., 2009). In contrast to patients with body-first PD, where the vagus and autonomic nuclei in the brainstem are heavily impacted, it is hypothesized that brain-first PD patients experience fewer symptoms resulting from autonomic dysfunction. For example, some groups have found that a subset of early-stage PD patients lack the de-innervation of cardiac sympathetic neurons typically observed in body-first PD using ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy (Kashihara et al., 2010; Kim et al., 2017). More recently, a cohort of 37 PD patients, subdivided based on a brain-first or body-first clinical presentation, were evaluated by MIBG scintigraphy and ^{18}F-dihydroxyphenylalanine (FDOPA) positron emission tomography (PET) imaging to evaluate dopamine in the putamen (Horsager et al., 2020). While both cohorts showed a similar loss of FDOPA PET in the putamen compared to control patients, the body-first PD patients showed a greater loss of sympathetic cardiac innervation and an increase in colon transit time and colon volume.

As the concept that PD is a disorder with at least two origins in the human body has gained support, it is becoming increasingly clear that a clinical tool for differentiating between these two patient groups is needed. In body-first PD, spreading of α-synuclein prions (or self-templating α-synuclein aggregates, sometimes referred to as prion-like α-synuclein) into the pons before the substantia nigra results in the pre-motor appearance of REM sleep behavior disorder (RBD) (Horsager et al., 2020; McKenna and Peever, 2017; Dauvilliers et al., 2018). Conversely, brain-first PD patients, who develop α-synuclein pathology in the substantia nigra prior to any potential brainstem involvement, develop motor symptoms prior to the possible onset of RBD (Horsager et al., 2020). Similarly, skin biopsies from a subset of isolated RBD (iRBD) patients were found to contain phosphorylated α-synuclein, whereas biopsies from almost all PD patients were immuno-positive, underscoring the peripheral origins of α-synuclein pathology in body-first PD patients (Miglis et al., 2021). While longitudinal studies are needed, the combination of RBD onset and skin biopsies may offer a way to predict which RBD patients are likely to phenoconvert to PD. Notably, when the presence of RBD was used to stratify diagnosed PD patients into two subtypes, RBD-positive patients appeared to present with a more malignant phenotype and faster disease progression, and have an increased burden of α-synuclein neuropathology at autopsy, compared to RBD-negative patients (Fereshtehnejad et al., 2015; Postuma et al., 2015). The initial findings that α-synuclein pathology is more widespread and severe in both the CNS and peripheral nervous system (PNS) of RBD-positive PD patients support the idea that PD patients should be categorized into brain-first and body-first subtypes. Moreover, these findings also suggest a need to differentiate between experimental data based on which PD subtype the model is replicating.

3. Creutzfeldt–Jakob disease – a disease with multiple origins

PrP^{C} is a cellular glycoprotein with a disordered N-terminus and a globular C-terminus with three α-helices and very little β-sheet structure. It is attached by a glycosylphosphatidylinositol-anchor to the outer cell membrane of neurons and a few other cell types (Stahl et al., 1987; Zahn et al., 2000; Colby and Prusiner, 2011). In contrast, PrP^{Sc} consists only of β-sheet structure, forms oligomers and amyloid fibrils, and is infectious

(Spagnolli et al., 2019; Kraus et al., 2021). When prions multiply, aggregated PrP^{Sc} molecules bind to and serve the newly recruited PrP^{C} molecules as a template for conformational change (Fig. 1). The newly converted PrP^{Sc} molecules inherit the same conformation, and therefore the biochemical and pathogenic properties of the parent PrP^{Sc} molecules, as well. This inheritance mechanism defines prion strains.

This prion mechanism is seen across multiple wild and domesticated animal species. Scrapie in sheep and goats, for instance, was discovered in the early 18th century, and CWD in deer and elk was first identified in 1967 (Williams and Young, 1980). Scrapie and CWD prions do not seem to harbor any zoonotic potential as no confirmed human transmission has been reported to date (Nemani et al., 2020). However, with the rise of industrialized meat production, BSE, a prion disease of cattle that is commonly known as mad cow disease, was first observed in the United Kingdom (UK) in 1986 (Wells et al., 1987). It was transmitted among cattle by the use of BSE-tainted meat-and-bone meal as feed. The BSE crisis culminated in the transmission of BSE to humans in the form of vCJD through the likely consumption of beef products contaminated with BSE prions (Will et al., 1996).

Sporadic CJD (sCJD) and vCJD belong to the larger group of human prion diseases. They are both caused by the misfolding and aggregation of human PrP^{C} but result in two distinct disease phenotypes (Hermann et al., 2021; Watson et al., 2021). With an incidence of 1–2 per million, human prion diseases are rare (Uttley et al., 2020). sCJD amounts to 85% of all CJD cases, and arises due to stochastically rare PrP misfolding and aggregation, which explains its late onset. The median age at death is 68 years following a median disease duration of 4 months (Unit TNCRS, 2020). Most remaining cases are due to mutations in the *PRNP* gene encoding for PrP, resulting in genetic CJD, Gerstmann-Sträussler-Scheinker syndrome, or fatal familial insomnia (Watson et al., 2021). Less than 1% of all CJD cases are acquired and have been caused either by accidental transmission of sCJD (for instance, by using contaminated dura mater or corneal grafts, or treatment of children with contaminated growth hormone isolated from the hypophyses of cadavers) resulting in iatrogenic CJD (Brown et al., 2012), or by infection with BSE resulting in vCJD (Will et al., 1996).

Since its first discovery in 1996, 232 cases of vCJD have been reported in 12 countries, of which 178 cases originated in the UK (Watson et al., 2021). While sCJD progresses faster and occurs in older individuals, the median age at death for vCJD is 28 years old, and patients have a longer median disease duration of 14 months (Unit TNCRS, 2020). Neurologically, sCJD is characterized by a rapidly progressing dementia with cerebellar and extrapyramidal signs, myoclonus, and visual symptoms. Patients with vCJD differ from the clinical presentation of sCJD and often display early signs of psychiatric problems before developing cognitive impairment, ataxia, and movement disorders. Neuropathologically, brains of sCJD and vCJD patients display white matter loss, fulminant neuroinflammation accompanied by astrogliosis and microgliosis, and neuronal vacuoles, which is why prion diseases are also referred to as transmissible spongiform encephalopathies. PrP^{Sc} also forms extracellular deposits, however, plaques in the brain are rarer in sCJD than in vCJD (Kitamoto et al., 1986). Characteristically, PrP^{Sc} plaques in vCJD brains are frequently surrounded by vacuoles, and are therefore referred to as florid plaques (Will et al., 1996).

While blood plasma of some patients with sCJD can harbor infectivity, there are no reported cases of iatrogenic transmission of sCJD based on blood products (Douet et al., 2014). In contrast to sCJD, there are five confirmed cases of vCJD transmission after blood transfusion with non-leukoreduced red blood cells from donors who developed vCJD several years after the donation, suggesting that the prevalence of vCJD prions in blood is higher (Urwin et al., 2016; Seed et al., 2018; DoHaS, 2019).

Biochemically, sCJD and vCJD prions can be distinguished based on their differential resistance to proteolytic digestion, as detected by western blot (Collinge et al., 1996). Analysis of patient brain homogenates after proteinase K digestion with antibodies against PrP results in three protease-resistant PrP^{Sc} fragments that differ in molecular size and abundance, providing a molecular fingerprint of the respective prion strain. While this molecular fingerprint differs for sCJD and vCJD prions, it does not for vCJD and BSE prions, indicating that they represent the same prion strain (Collinge et al., 1996). Strain identity of vCJD and BSE prions is also supported by transmission experiments to wild-type (WT) and transgenic (Tg) mice expressing human PrP, which result in similar incubation times and attack rates (Hill et al., 1997). Notably, these both differ from transmission studies using sCJD prions.

As outlined above, multiple lines of evidence demonstrate that sCJD and vCJD prions possess different biochemical and pathogenic properties that are conformationally encoded by two distinct PrP^{Sc} strains (Spagnolli et al., 2019; Kraus et al., 2021; Collinge et al., 1996). Given the noted differences in sCJD and vCJD, it is important that model systems account for these differences in disease etiology.

4. Investigating neuroinvasion in animal models of disease

4.1. Body-first Parkinson's disease

Several animal models have been used to investigate the spread of α-synuclein prions from the ENS to the CNS in body-first PD. In 2000, Betarbet *et al.* showed that chronic intravenous delivery of the pesticide rotenone, which disrupts the mitochondrial complex I electron transport chain, induces a parkinsonian phenotype in Sprague Dawley rats (Betarbet et al., 2000). The observed motor deficits are accompanied by the loss of dopaminergic neurons in the substantia nigra and ubiquitinated α-synuclein inclusions in the brain. Building from this discovery, Pan-Montojo *et al.* used oral gavage of rotenone to induce inflammation and α-synuclein pathology in the ENS, which they found spread to the DMV in the brainstem (Pan-Montojo et al., 2010). Notably, the spreading of α-synuclein prions along synaptically connected circuits was induced by concentrations of rotenone so low that the compound could not be detected in systemic blood or CNS samples collected from dosed animals. Consistent with the hypothesis that PD originates in the gastrointestinal tract and spreads into the CNS via the vagus, subsequent studies by the same group found that both hemi-vagotomy and partial sympatectomy in mice given rotenone via oral gavage prevented the previously observed neuroinvasion of α-synuclein prions (Pan-Montojo et al., 2012).

Along with pesticides, the microbiome in the gastrointestinal tract is also hypothesized to play a role in body-first PD (reviewed in (Miraglia and Colla, 2019)). Chen *et al.* investigated this possibility by feeding *Escherichia coli* (*E. coli*) to aged Fischer 344 rats, as well as *C. elegans* expressing human α-synuclein (Chen et al., 2016). It is well-established that bacteria express extracellular amyloid proteins that play important roles in biofilm production in addition to host invasion and adherence (Hufnagel et al., 2013; Larsen et al., 2007). The *E. coli* protein curli, the best studied of these bacterial amyloids, contains imperfect glutamine and asparagine-rich repeats, raising the possibility of cross-seeding between the amyloidogenic proteins. After antibiotic treatment to clear the microbiomes of the Fischer 344 rats, animals were orally dosed weekly with *E. coli* either lacking (mutant) or retaining (WT) the two curli operons for two months (Chen et al., 2016). Neuropathological analysis of brain tissue showed that rats fed WT *E. coli* developed α-synuclein inclusions in the hippocampus and striatum, as well as microglial hyperplasia and an increase in astrocyte immunolabeling. In comparison, the same neuropathological changes were absent in mice fed mutant *E. coli* unable to express curli. Similar observations were reported in *C. elegans*; *E. coli* expressing curli induced α-synuclein aggregate formation in the head of *C. elegans*, whereas the mutant *E. coli* had no effect. These initial studies contribute to a growing body of work investigating the role of the microbiome in the gut-brain axis in PD. For example, Sampson *et al.* reported that recolonizing the gut of Tg mice overexpressing human α-synuclein with the microbiota from PD patients exacerbated motor impairment compared to microbiota from healthy patients (Sampson

et al., 2016).

In addition to toxin- and bacteria-induced models, several Tg rodents that use CNS-predominant promoters to overexpress either WT or mutant human α-synuclein in the brain and spinal cord have been established to investigate the role of α-synuclein aggregation in PD pathogenesis (Masliah et al., 2000; van der Putten et al., 2000; Giasson et al., 2002; Fleming et al., 2004; Gispert et al., 2003; Gomez-Isla et al., 2003; Ikeda et al., 2009; Kahle et al., 2000; Lee et al., 2002; Liu et al., 2010; Rockenstein et al., 2002; Sharon et al., 2003; Zhou et al., 2008; Kahle et al., 2002; Shults et al., 2005; Yazawa et al., 2005; Kuo et al., 2010). While these studies have been important for investigating the process of transsynaptic spread of α-synuclein prions throughout the brain, they have largely failed to replicate the PNS origins of disease in body-first PD patients. The first models to overcome this limitation were the Tg(*SNCA*$^{+/+}$,*Snca*$^{-/-}$) mouse models generated by Robert Nussbaum's group (Kuo et al., 2010). Rather than using a CNS-specific promoter, human α-synuclein was cloned into a P1 artificial chromosome that also includes the upstream and downstream regulatory elements of the entire gene. This approach is thought to result in an expression profile that more closely resembles α-synuclein expression in the human body. Comparing mice expressing either WT or the PD-causing A53T and A30P mutations, the authors found that A53T and A30P mice showed a reduction in colonic motility that was more pronounced in male mice compared to females starting at 3 months of age. This dysfunction preceded the motor deficits detected in the A53T mouse line by rotarod at 6 months of age.

Injection models have also been used to study the route of α-synuclein spread from the ENS into the CNS, though it is important to note that these models rely on direct injection of α-synuclein into the nerve fibers and neurons of the ENS in the gut wall. Homogenates prepared from deceased PD patient samples and recombinant α-synuclein preformed fibrils (PFFs) injected into the wall of the stomach and duodenum near the myenteric (Auerbach's) plexus were transported along the vagus nerve to the DMV in Sprague Dawley rats (Holmqvist et al., 2014). More recently, Uemura *et al.* injected PFFs into the gastric wall of C57BL/6J mice and detected α-synuclein aggregates in the DMV 45 days post-injection (dpi) (Uemura et al., 2018). Intriguingly, injection of PFFs into the duodenal wall of aged mice, but not young animals, resulted in the spread of neuropathology to the midbrain, and the subsequent onset of motor deficits (Challis et al., 2020). Critically, when mice were injected with PFFs after receiving a vagotomy, spreading of α-synuclein pathology to the DMV was prevented, demonstrating that neuroinvasion from the ENS occurred via the vagus nerve. Similar studies injecting PFFs into the duodenal and pyloric muscularis layer in C57BL/6J mice also found that a truncal vagotomy prevented the gut-to-brain spread of α-synuclein pathology (Kim et al., 2019). However, neuroinvasion was blocked when PFF injections were performed in an α-synuclein knockout mouse model, demonstrating that this phenomenon is α-synuclein-dependent. These conclusions are supported by studies using adeno-associated virus vectors (AAVs) to express human α-synuclein in Sprague-Dawley rats (Ulusoy et al., 2013). Unilateral injection of the AAVs into the left vagus at the level of the neck resulted in retrograde transport of α-synuclein to the medulla, and subsequent caudal to rostral spread of neuropathology throughout the brainstem and into the midbrain and forebrain. Combined, these studies underscore the critical role that the vagus nerve plays in neuroinvasion in body-first PD.

Similar transmission experiments have also been conducted using Tg animal models. The TgM83$^{+/-}$ mouse model, which uses the *Prnp* promoter to express human α-synuclein with the A53T mutation (Giasson et al., 2002), is a frequently used mouse model of synucleinopathy. Notably, while homozygous TgM83$^{+/+}$ mice develop spontaneous disease, the hemizygous mice only develop neurological signs following injection of α-synuclein prions (Watts et al., 2013). PFFs injected either into the tongue or the peritoneal cavity of TgM83$^{+/-}$ mice resulted in neuroinvasion and disease onset 285 and 229 dpi, respectively (Breid et al., 2016). Symptomatic mice exhibited robust phosphorylated α-synuclein neuropathology in the brain and spinal cord. Others have also observed neuroinvasion in the model following intraperitoneal and hind leg injections of PFFs (Ayers et al., 2017; Sacino et al., 2014). More recently, neuroinvasion and disease onset were observed following oral gavage and intravenous injection of PFFs into TgM83$^{+/-}$ mice (Lohmann et al., 2019). Notably, all four of these studies showed that challenging TgM83$^{+/-}$ mice with PFFs in the periphery resulted in the spreading of α-synuclein pathology into the brainstem, consistent with the hypothesized route of spread in body-first PD. To control for the possibility that trauma from the injections themselves induced α-synuclein misfolding and spreading, negative control injections were performed using bovine serum albumin, lipopolysaccharide, keyhole limpet hemocyanin, or Dulbecco's phosphate-buffered saline. The lack of neuropathological inclusions or disease in mice injected with these controls (Breid et al., 2016; Ayers et al., 2017; Sacino et al., 2014; Lohmann et al., 2019) indicates the reported results are caused by α-synuclein self-templating, rather than trauma at the injection site.

Expanding on these findings, Van Den Berge *et al.* used the rat BAC model, which was generated by cloning WT human α-synuclein with the endogenous regulatory elements into a bacterial artificial chromosome (Nuber et al., 2013), to investigate the route of spread of α-synuclein prions following PFF injections into the wall of the pylorus and duodenum (Van Den Berge et al., 2019). Two- and four-months post-injection, α-synuclein pathology was observed throughout the vagus nerve and the DMV, demonstrating spreading along parasympathetic fibers, as well as in the intermediolateral cell column (IML), showing propagation along sympathetic nerve fibers. PFF-injected rats also had extensive α-synuclein pathology within the myenteric plexus in the stomach, as well as in myocardial ganglia and neurites. This latter observation is consistent with the MIBG scintigraphy data from PD patients discussed above.

While rodent models have been important for establishing the role of α-synuclein prion spread from the periphery to the brain in body-first PD, recent studies have contributed new insights into the origin of misfolded α-synuclein in the gut. Research from Rodger Liddle and colleagues led to the discovery that enteroendocrine cells (EECs) in the gut epithelium not only express α-synuclein, but also exhibit a number of neuron-like properties (Chandra et al., 2017). EECs, which face the lumen of the gut, have axon-like processes on the basal surface of the cell that connect with enteric neurons expressing α-synuclein (Bohorquez et al., 2015). Moreover, EECs express presynaptic proteins, as well as neurofilaments, and are excitable, indicating they may exhibit a similar functionality as neurons (Bohorquez et al., 2014). While further investigation into the role of EECs in PD is needed, this important discovery raises the possibility that toxins and bacteria in the lumen of the gut may induce α-synuclein misfolding in EECs, which then interact directly with enteric neurons known to synapse with autonomic fibers in the vagus.

Finally, non-human primates have also been used to develop a model of body-first PD (Arotcarena et al., 2020). Working with baboon monkeys, Arotcarena *et al.* isolated LB extracts containing α-synuclein prions from PD patient samples, which they injected into the stomach and duodenum ventral wall. Two years later, the authors reported a reduction in tyrosine hydroxylase-positive neurons in the substantia nigra and mild α-synuclein neuropathology in a handful of brain regions, including the parahippocampal cortex. While the monkeys had significant α-synuclein immunostaining in the gut, no inclusions were observed in the vagus nerve. Additional studies using non-human primates are needed to further investigate the role of non-vagal routes of neuroinvasion in body-first PD.

4.2. Peripheral transmission of BSE and vCJD prions

The rarity of vCJD has made it difficult to assess the spatiotemporal propagation of BSE/vCJD prions from the periphery into the CNS in humans after infection. Important insights about possible routes of neuroinvasion and the tissues involved originate from studies in various

animal species that have been peripherally infected with BSE or scrapie prions, including rodents, sheep, cattle, and non-human primates (van Keulen et al., 2008; Lasmézas, 2017; Wells et al., 1994; Barlow and Middleton, 1990).

While oral transmission of BSE/vCJD prions to WT rodents is possible, the routes along which BSE/vCJD prions propagate prior to neuroinvasion have not been investigated in detail (Barlow and Middleton, 1990). However, oral transmission studies of scrapie prions to mice and hamsters have provided important insights regarding the routes along which PrP^{Sc} *can* propagate into the CNS (Kimberlin and Walker, 1989; Beekes et al., 1996; Baldauf et al., 1997; Beekes et al., 1998; McBride and Beekes, 1999; Beekes and McBride, 2000; McBride et al., 2001). In orally infected mice and hamsters, PrP^{Sc} was first detected in gut-associated lymphoid tissues such as the Peyer's patches and the submucosal (Meissner's) and myenteric plexuses of the ENS (Beekes and McBride, 2000; McBride et al., 2001). After accumulation in the ENS, PrP^{Sc} was discovered to spread along two pathways from the gut to the brain. In the first pathway, PrP^{Sc} was discovered to spread from the small intestine along the parasympathetic nervous system via retrograde transport along the vagus nerve to the DMV in the brainstem (Baldauf et al., 1997; Beekes et al., 1998; McBride et al., 2001). In the second pathway, PrP^{Sc} was transported along the sympathetic nervous system to the IML in the thoracic spinal cord. Retrograde transport via efferent nerve fibers was found to relay PrP^{Sc} first to the celiac and mesenteric ganglion complex (CMG) and then via the splanchnic nerves, which mediate sympathetic innervation of the gastrointestinal tract, to the IML from where they were observed to ascend along the spinal cord to the brain (McBride and Beekes, 1999; McBride et al., 2001).

Sheep and goats are susceptible to oral infection with BSE prions (Foster et al., 1993). Notably, a similar spatiotemporal spread of PrP^{Sc} from the gut to the CNS as in scrapie-infected hamsters and BSE-infected cattle has been observed in oral transmission studies of BSE prions to sheep that were killed at various time points after infection (van Keulen et al., 2008). Sheep orally infected with BSE prions accumulated PrP^{Sc} in secondary lymphoid tissues of the gut, followed by lymph nodes draining these and the spleen, and later in lymph nodes not associated with the gut. PrP^{Sc} was also detected in macrophages of the marginal zone of germinal centers, indicating trapping and phagocytosis of systemically circulating BSE prions (Houston et al., 2008). In the PNS, PrP^{Sc} was first seen in post-ganglionic parasympathetic neurons in the submucosal and myenteric plexuses of the ENS and post-ganglionic sympathetic neurons in the CMG. In the CNS, PrP^{Sc} was first observed in pre-ganglionic parasympathetic neurons of the DMV and in pre-ganglionic sympathetic neurons of the IML, indicating that BSE prions propagate from the ENS along efferent fibers of the autonomic nervous system (ANS) to the CNS, as seen during the pathogenesis of natural scrapie in sheep (van Keulen et al., 2000).

Studies in cattle that were killed at successive time points after oral infection showed that classical BSE prions propagate by retrograde spread along two routes from the gastrointestinal tract to the CNS, both of which involve the ANS (Hoffmann et al., 2007; Kaatz et al., 2012; Hoffmann et al., 2011). In one pathway, BSE prions spread from the Peyer's patches of the small intestine via the CMG and splanchnic nerves to the lumbar and caudal thoracic spinal cord, and subsequently along the spinal cord to the brain. In the second pathway, BSE prions spread along the vagus nerve to the DMV in the brainstem (Hoffmann et al., 2007). The observation that the dorsal root ganglia were only affected later in disease suggests that prion invasion of the somatic nervous system, e.g. the sciatic nerve, is a secondary retrograde event following prion replication in the CNS, which is also seen in BSE-infected cynomolgus macaques (*Macaca fascicularis*) (Hoffmann et al., 2007; Herzog et al., 2004).

Cynomolgus macaques, a non-human primate species, represent the closest animal model used to study BSE transmission to humans. Intracerebral transmission of classical BSE prions to cynomolgus macaques causes disease with clinical, neuropathological, and molecular features that are very similar to vCJD in humans, providing evidence that BSE and vCJD are caused by the same prion strain (Lasmézas et al., 1996). Peripheral transmission by oral or intravenous challenge with classical BSE prions also causes disease in cynomolgus macaques and shows that prions readily propagate to the CNS from the periphery, including through the gastrointestinal tract (Herzog et al., 2004; Lasmézas et al., 2005; Holznagel et al., 2013). While incubation periods for intravenous transmission were shorter than those for oral challenge, the distribution of PrP^{Sc} pathology in clinically diseased animals was similar for both inoculation routes (Herzog et al., 2004). PrP^{Sc} was detected in lymphoreticular tissues, such as spleen and tonsils (Bruce et al., 2001), and was localized to the germinal centers, as is seen in vCJD patients, with intravenous transmission leading to higher titers of PrP^{Sc} than oral transmission (Herzog et al., 2004; Hill et al., 1999). Additionally, PrP^{Sc} was found in secondary lymphoid tissues, such as isolated follicles and Peyer's patches of the gastrointestinal tract from the duodenum to the rectum, and has been detected in both plexuses of the ENS, small sympathetic nerve fibers innervating the inner smooth muscle layer, and in nerve fibers of the lamina propria of the intestinal villae (Herzog et al., 2004). Moreover, PrP^{Sc} was also detected in motor nerves, including the sciatic nerve, and in autonomic nerves at the surface of Schwann cells (Herzog et al., 2004).

Although animal models have been very helpful to elucidate possible routes along which vCJD/BSE prions propagate to reach the CNS after peripheral exposure, some differences may exist between prion propagation in humans and animals. In contrast to vCJD patients, vCJD/BSE-infected cynomolgus macaques, and BSE-infected sheep, BSE prions have so far not been detected in the blood of BSE-infected cattle, which may be due to a differential expression of PrP^{C} or other molecules that confer binding of PrP^{Sc} in blood cells of primates and sheep (Houston et al., 2008; McDowell et al., 2015; Balkema-Buschmann et al., 2021).

5. Similarities and differences between α-synuclein and PrP^{Sc} neuroinvasion

A combination of experimental studies and data collected from body-first PD and vCJD patients suggest the two diseases rely on overlapping routes of neuroinvasion through the ANS (Fig. 2). Starting in the gastrointestinal tract, phosphorylated α-synuclein has been detected in PD patients up to 20 years before the onset of motor symptoms (Beach et al., 2010; Gelpi et al., 2014). Interestingly, pathogenic α-synuclein has been observed in the appendix of healthy individuals, and while conflicting results have been reported, some groups have observed that an appendectomy can be protective against PD (Marras et al., 2016; Mendes et al., 2015; Killinger et al., 2018; Svensson et al., 2016; Yilmaz et al., 2017). The formation of pathogenic α-synuclein in the gastrointestinal tract may be mediated by rotenone exposure, amyloidogenic bacterial proteins or infection, spontaneous α-synuclein misfolding, or other mechanisms. Recent studies identifying α-synuclein expression in the EECs lining the lumen of the gut (Liddle, 2018; Chandra et al., 2017) offer one possible route of spread to the myenteric plexus and/or the submucosal plexus, which often contain LBs in PD patients (Wakabayashi et al., 1988). From these plexuses, α-synuclein is able to propagate and spread into the ANS (Chandra et al., 2017; Braak et al., 2003b; Phillips et al., 2008).

On the parasympathetic side, spread of α-synuclein through the vagus results in LB pathology in the DMV in the brainstem, resulting in RBD (Horsager et al., 2020; McKenna and Peever, 2017; Dauvilliers et al., 2018), as discussed earlier. From the DMV, α-synuclein spreads to the raphe nuclei and locus coeruleus (Ter Horst et al., 1991; Westlund and Coulter, 1980; Rogers et al., 1980), and then on to the substantia nigra (Wang et al., 2014), where the loss of dopaminergic neurons plays a dominant role in the overt motor deficits seen in PD patients. Investigating involvement from the sympathetic branch, a detailed analysis of LB distribution in 15 deceased PD patients found LBs in the stellate and sympathetic ganglia, as well as the heart, of 100% of cases (Gelpi et al.,

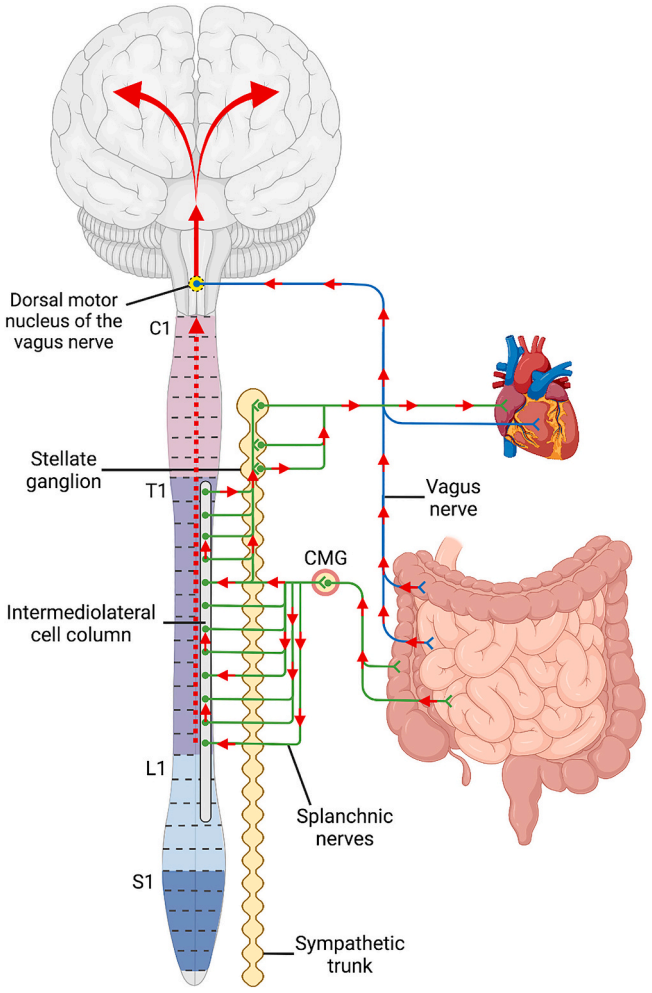

Fig. 2. Spreading of α-synuclein and vCJD prions via the autonomic nervous system to the brain and visceral organs

Neuroinvasion to the brain by α-synuclein and vCJD prions from the gastrointestinal tract is mediated by both the parasympathetic (blue) and sympathetic (green) branches of the autonomic nervous system. During parasympathetic spread, α-synuclein and vCJD prions reach the dorsal motor nucleus of the vagus (DMV) in the brainstem by retrograde transport along the vagus nerve. Further propagation within the brain is mediated through transsynaptic spread, and for α-synuclein prions, follows Braak staging of disease. A comparable, concise staging of brain pathology for vCJD prions is not available due to their rapid propagation within the brain and relatively smaller number of cases. During sympathetic spread, α-synuclein and vCJD prions are retrogradely transported via postganglionic fibers from the celiac and mesenteric ganglion complex (CMG) to the ganglia, where they undergo transsynaptic transport to reach the splanchnic nerves. Retrograde transport along the splanchnic nerves brings α-synuclein and vCJD prions to the respective cell bodies of the axonal efferents within the intermediolateral cell column (IML) of the spinal cord. Within the IML and spinal cord, vCJD prions spread and ascend along the spinal cord to the brain; this pattern of spread has not yet been described in detail for α-synuclein prions. From the IML, α-synuclein and vCJD prions are anterogradely transported via axonal efferents to ganglia within the sympathetic trunk. Although vCJD prions have been detected in the heart, only spreading of α-synuclein prions via efferents of the stellate and cervical ganglia has been reported. From there, transsynaptic transport via efferents of these ganglia to the heart has been described. Additional anterograde transport along efferents from other ganglia within the IML, the sympathetic trunk, and the DMV leads to a late and more general spread to additional visceral organs. Created with BioRender.com.

2014). These data are consistent with the idea that α-synuclein prion spreading through the ANS into the IML mediates the loss of sympathetic innervation to the heart, as detected by MIBG scintigraphy (Horsager et al., 2020; Kashihara et al., 2010; Kim et al., 2017). Notably, the IML is directly connected to the locus coeruleus (Westlund and Coulter, 1980; Bruinstroop et al., 2012), as well as the reticular formation (Del Tredici and Braak, 2012; Hornung, 2003), suggesting it is possible that α-synuclein can reach the brain through the sympathetic branch. However, it is quite rare to find LB pathology in the spinal cord but not the brainstem and brain (Del Tredici and Braak, 2012; Bloch et al., 2006; Sumikura et al., 2015), suggesting that LB spread into the brain is more likely to occur via the parasympathetic branch.

In vCJD, PrP^{Sc} inclusions accumulate outside the CNS in a number of secondary lymphoid tissues, including the spleen, palatine tonsils, lymph nodes, ilial Peyer's patches, appendix, and rectum (Bruce et al., 2001; Hill et al., 1999; Hilton et al., 1998; Ironside et al., 2000; Wadsworth et al., 2001; Hilton et al., 2004a; Hilton et al., 2004b; Will, 2014). Immunohistochemical analysis of appendectomy samples in the UK have also revealed the presence of abnormal PrP in healthy individuals, suggesting that they may have subclinical infections (Hilton et al., 2004a; Gill et al., 2013; Gill et al., 2020). Based on the demographics of the BSE epidemic and the subsequent occurrence of vCJD cases, incubation periods in infected individuals may be as long as several decades, and may even surpass incubation times for body-first PD, which is thought to take up to 20 years (Watson et al., 2021; Unit TNCRS, 2020; Beach et al., 2010; Gelpi et al., 2014). More recent transmission studies with tissue homogenates from four vCJD patients to Tg mice expressing bovine PrP, which are susceptible to infection with vCJD prions, have shown that considerably more non-CNS tissue types harbor infectivity, albeit at variable and lower concentrations, including the ovary/testis, skeletal muscle, bone marrow, adrenal gland, thyroid, pancreas, salivary gland, kidney, liver, lung, thymus, spleen, and heart (Douet et al., 2021). Surprisingly, the same study detected a very similar tissue distribution for sCJD prions by transmission to Tg mice expressing human PrP (Douet et al., 2021). These findings suggest that sCJD prions can spread from the CNS to the periphery, just as vCJD prions spread from the periphery to the CNS, paralleling the spread of α-synuclein prions in both brain-first and body-first PD.

Within secondary lymphoid tissues of the gut, vCJD prions are detected in follicular dendritic cells within germinal centers, where PrP^{C} is also expressed (Thielen et al., 2001). Gut-associated lymphoid tissues are highly innervated with sympathetic fibers, and PrP^{C} is also expressed in the ENS (Shmakov et al., 2000). Because only a thin layer of intestinal epithelial cells separates ingested BSE prions from host PrP^{C} in enteric nerve endings, these areas are potential entry sites for BSE prions to the ANS (Shmakov et al., 2000). Identification of vCJD prions in sympathetic celiac, superior mesenteric, and stellate ganglia indicate that vCJD prions retrogradely propagate via efferents of the CMG and the splanchnic nerves from the enteric plexuses of the gut to the IML in the spinal cord, and via anterograde transport from there to the stellate and other ganglia in the sympathetic trunk (Ironside et al., 2000; Haik et al., 2003). Detection of vCJD prions in heart tissue suggests that they may reach the heart by anterograde transport via the stellate ganglia (Douet et al., 2021; Haik et al., 2003), as is seen in body-first PD.

On the parasympathetic side, direct evidence for retrograde transport of BSE/vCJD prions along the vagus nerve from the enteric plexuses of the gut to the DMV in the brainstem is still missing, but it has been hypothesized based on findings in other animal models following peripheral transmission and neuroinvasion of PrP^{Sc} (Pomfrett et al., 2007). Additionally, detection of PrP^{Sc} in the DMV and the vagus nerve of patients with sCJD and genetic CJD indicates that the vagus nerve can serve as a conduit for the transport of prions and may do so during the spread of vCJD prions originating in the gut (Kresl et al., 2019). Once vCJD prions have reached the DMV, prion pathology is thought to spread more diffusely within the brain in vCJD and, therefore, may be less associated with specific anatomical pathways compared to sCJD

(Ironside et al., 2000; Armstrong et al., 2003; Armstrong et al., 2009).

There are, of course, other possible routes of neuroinvasion for both body-first PD and vCJD, with some similarities and differences between the two. Radiolabeled α-synuclein injected systemically into CD-1 mice was able to cross the blood–brain barrier, demonstrating that α-synuclein may be able to enter the CNS through circulating blood (Sui et al., 2014). This is consistent with inoculation studies in TgM83 mice showing systemic delivery of PFFs results in neurological disease and widespread CNS pathology (Ayers et al., 2017; Lohmann et al., 2019). Notably, α-synuclein is expressed at high levels in red blood cells (Barbour et al., 2008), supporting the feasibility of systemic spreading. Injection of PFFs into the tongue or the peritoneal cavity also results in disease, as well as α-synuclein inclusions throughout the CNS and spinal cord (Breid et al., 2016). While the autonomic pathways discussed above may contribute to disease in these animals, it is also quite likely that a α-synuclein prions use other neuronal routes of entry, as well. Direct injection of PFFs into the sciatic nerve of Tg mice resulted in transsynaptic α-synuclein prion spreading through the dorsal root ganglion and the spinal cord to reach the brain (Ayers et al., 2018).

As mentioned earlier, vCJD can also be transmitted by blood transfusion (Unit TNCRS, 2020; Urwin et al., 2016; Seed et al., 2018). Transmission of BSE prions to sheep parallels that to humans with regard to the subsequent tissue distribution of infectivity (Houston et al., 2000). Transfusion studies using blood components of sheep orally infected with BSE prions have shown that prion infectivity in sheep is associated with plasma, platelets, red blood cells, and white blood cells (Salamat et al., 2021). Moreover, oral transmission studies of mouse-adapted and radiolabeled scrapie prions in C57BL/6 mice have shown that PrP^{Sc} can readily cross the intestinal barrier and reach the brain via the hematogenous route in quantities that are theoretically sufficient to induce prion replication in the brain without having to propagate along the ANS first (Urayama et al., 2016). Radiolabeled scrapie prions have also been used to demonstrate that PrP^{Sc} can readily cross the blood brain barrier (Banks et al., 2004). Whether this is also the case for BSE/vCJD prions after oral ingestion or blood transfusion is unclear. However, neuropathological analysis of vCJD brains, where transmission likely occurred after oral ingestion, does not indicate a spatial relationship between the pathological features of vCJD and blood vessels. This suggests that neuroinvasion most likely occurs via the ANS after oral ingestion (Armstrong et al., 2003).

6. Conclusions

In both body-first PD and vCJD, self-templating of either misfolded α-synuclein or PrP^{Sc}, respectively, enables the spread of disease from the periphery into the CNS. Once α-synuclein and PrP^{Sc} prions enter the brain, they are able to propagate and cause the progressive degeneration characteristic of the two disorders. While many routes of neuroinvasion likely contribute to disease pathogenesis, there is strong evidence from both experimental models and human patients that the ANS serves as a critical conduit to the brainstem from the gut. A growing number of studies indicate that in a subset of PD patients, α-synuclein misfolding originates in the gut, whether spontaneous, induced by changes in the microbiota, or other causes, and that spreading from the gut to the CNS is mediated by the ANS. Similar data for vCJD indicates that following peroral exposure to BSE prions, neuroinvasion of PrP^{Sc} can occur via retrograde propagation through both the sympathetic and parasympathetic branches. While less overlap is seen for other pathways into the CNS between the two proteins, the overlapping role of the ANS suggests that future research should focus on investigating *how* neuroinvasion occurs via this mechanism. These important studies will likely yield novel therapeutic targets to prevent the progression of both diseases.

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