VIEWPOINT

The Heart of the Matter: Cardiac Denervation Casts Doubt on the Brain-First Versus Body-First Hypothesis of Parkinson's Disease

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Parkinson's disease (PD) is an increasingly common neurodegenerative disease that is pathologically characterized by preferential dopaminergic cell loss in the substantia nigra (SN) and the appearance of Lewy bodies (LBs) in other neurons. Braak and colleagues[1] have shown that the dorsal motor nucleus of the vagal nerve (DMV) in the medulla oblongata and the olfactory bulb (OB) are the two major sites of early LB formation. Further, the DMV has a higher burden of LB pathology than the upper brainstem, including the locus coeruleus and the SN in PD. Due to the caudorostral gradient of brainstem LBs, it has been hypothesized that the pathological process in PD begins in the lower brainstem and subsequently progresses in an ascending fashion. This is referred to as the Braak hypothesis.[1,2] Thereafter, Hawkes et al[3] refined this concept by incorporating the peripheral autonomic nervous system (PNS) and the OB, and they have proposed an in-depth hypothesis that neurotoxic pathogens (eg, viruses, pesticides, and air pollutants) enter the brain via two routes in the enteric nervous system (ENS) and the OB. This is referred to as the dual-hit hypothesis. Then, some experimental findings (eg, α-synuclein [aS] aggregates propagating from one cell to another) were integrated,[4] leading to a compelling hypothesis, in particular, that the pathophysiology of PD is governed unitarily by prion-like transmission of misfolded aS either from the brain or the gut (the brain-first vs. body-first PD hypothesis).[5,6] This conceptual framework has attracted significant attention with the expectation that transmissible aS species could be novel targets of neuroprotective therapies such as immunotherapy.[7] However, the notion that PD pathology can be explained solely by the spread of noxious aS remains a matter of debate[8-10] and has been mainly criticized for its oversimplification as an explanation for the complexity of actual PD pathology.[11] Recently, we reported that cardiac sympathetic denervation was associated with widespread cortical atrophy, but not with nigrostriatal neurodegeneration in PD.[12] The finding that neurodegeneration in PD occurs in both the PNS and central nervous system (CNS) independent of a midbrain lesion may support the idea of multifocal or diffuse pathological initiation rather than one-way propagation from a single origin. To address these issues, we discuss limitations of the brain-first versus body-first hypothesis in PD by focusing on the unique feature of cardiac sympathetic involvement.

Overview of the Site and Connectome Model

The aS origin site and connectome (SOC) model, which was proposed by Borghammer and colleagues,[5,13] is a recent topical hypothesis about prion-like spreading of aS pathologies in PD. In this model, interneuronal transmission of aberrantly misfolded aS plays a central role in PD pathogenesis.

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In addition, the phenotypic variability among patients with PD can be explained by the sites of the earliest onset of aS pathology and the neural connections extending from those sites. In particular, they hypothesized that aS misfolding originates from either the OB and/or amygdala in one cerebral hemisphere or the gut. Further, these two sites of origin correspond to the two distinct clinicopathological phenotypes of PD, which are the brain-first and body-first PD subtypes. The brain-first PD is a benign subtype in which LB pathology starts in the unilateral OB or amygdala and spreads to the ipsilateral SN and neighboring areas, followed by spread to various areas via the spinal cord and PNS. This subtype may have greater asymmetry in motor symptoms with predominantly unilateral distribution of aS pathology because of fewer interhemispheric connections in the brain. On the contrary, body-first PD is a malignant subtype in which aS pathology starts in the ENS and reaches to the bilateral DMV followed by caudorostral progression to upper brainstem and cortical areas.[14-16] Compared with brain-first PD, the pathological progression in this subtype is likely to be faster due to strong bidirectional connections from the gut to the CNS. Taking this idea a step further, it was hypothesized that the appearance of rapid eye movement-sleep behavior disorder (RBD), which may be related to LB pathology in the locus coeruleus, before parkinsonism indicates the body-first subtype (Fig. 1A).[6,13-16] Theoretically, the SOC model is a simple and plausible hypothesis that directly links the Braak dual-hit hypotheses with the prionoid nature of misfolded aS. However, this model is based on several unproven assumptions that (1) LB pathology starts at a single site of origin, (2) pathogenic aS propagates exclusively via intercellular transmission, and (3) RBD arises when aS pathology reaches the pons.[5,13,16] Furthermore, recent imaging studies focusing on the asymmetry of striatal dysfunction provide conflicting evidence against the SOC model.[9,17] Moreover, the mechanism behind cardiac sympathetic degeneration is not adequately considered in the SOC model. Thus, this should be further discussed.

Cardiac Sympathetic Degeneration in PD: Contradictions in the SOC Model

Cardiac sympathetic degeneration is the common and distinguishable feature of LB diseases from atypical parkinsonism. In the SOC model, the cardiac sympathetic nerves are interpreted to be one of the relay points from the gut to the brain. However, this notion may not be supported by the distribution of the aS pathology in PD. Postmortem studies focusing on the cardiac sympathetic nerves in PD have demonstrated that phosphorylated aS accumulates in the distal axons of cardiac sympathetic nerves before neuronal soma in the paravertebral sympathetic ganglia.[18] Further, simultaneous observations of cardiac sympathetic nerves and the spinal cord have shown that pathological aS density in the sympathetic ganglia was more severe than that in the intermediolateral nucleus (IML) of the spinal cord (Fig. 1B).[19,20] Moreover, there is a case of incidental LB disease in which the aS pathology was restricted to the heart and sympathetic ganglia.[21] These data strongly indicate that pathogenic aS deposits occur in the periphery of cardiac sympathetic nerves initially, then in the sympathetic ganglia, and further spread to the anatomically connected IML. However, in the SOC model, the only route for noxious aS propagation to cardiac sympathetic nerves could be from the IML in the spinal cord to postganglionic cardiac sympathetic nerves irrespective of the brain-first and body-first subtypes, which is inconsistent with the actual distribution in human pathology. This discrepancy arises because the SOC model attempts to explain the pathological progression of PD by neurogenous aS transmission either from the brain or the gut. However, it is more likely that the cardiac sympathetic nervous system is an independent starting point of aS pathology in PD.

Cardiac Sympathetic Nervous System as a Pathological Origin of LBs

The mechanism by which pathogenic changes start in the cardiac sympathetic nervous system in LB disease is still enigmatic. The parasympathetic nervous system can be a route of misfolded aS propagation to the periphery of cardiac sympathetic nerves, because cardiac sympathetic denervation likely occurs together with parasympathetic cholinergic denervation via the vagus nerve.[22-24] However, this progression pattern seems unlikely because (1) sympathetic and parasympathetic dysfunctions occur independently in the early phase of PD[24]; and (2) the burden of LB pathology in sympathetic ganglia exceeds that in the parasympathetic DMV,[22] which suggests that sympathetic degeneration precedes parasympathetic degeneration in PD.[25]

Recent studies have demonstrated pathogenic aS seeds in the blood of patients with LB diseases,[26,27] suggesting the possibility of systemic spread of misfolded proteins via the bloodstream. If such a propagation process exists, in addition to the OB/amygdala and ENS, the heart can be the initiation site of aS pathology. It has also been pointed out that pathological changes may begin in the distal part of the PNS of the skin or, more recently, the kidney,[28]

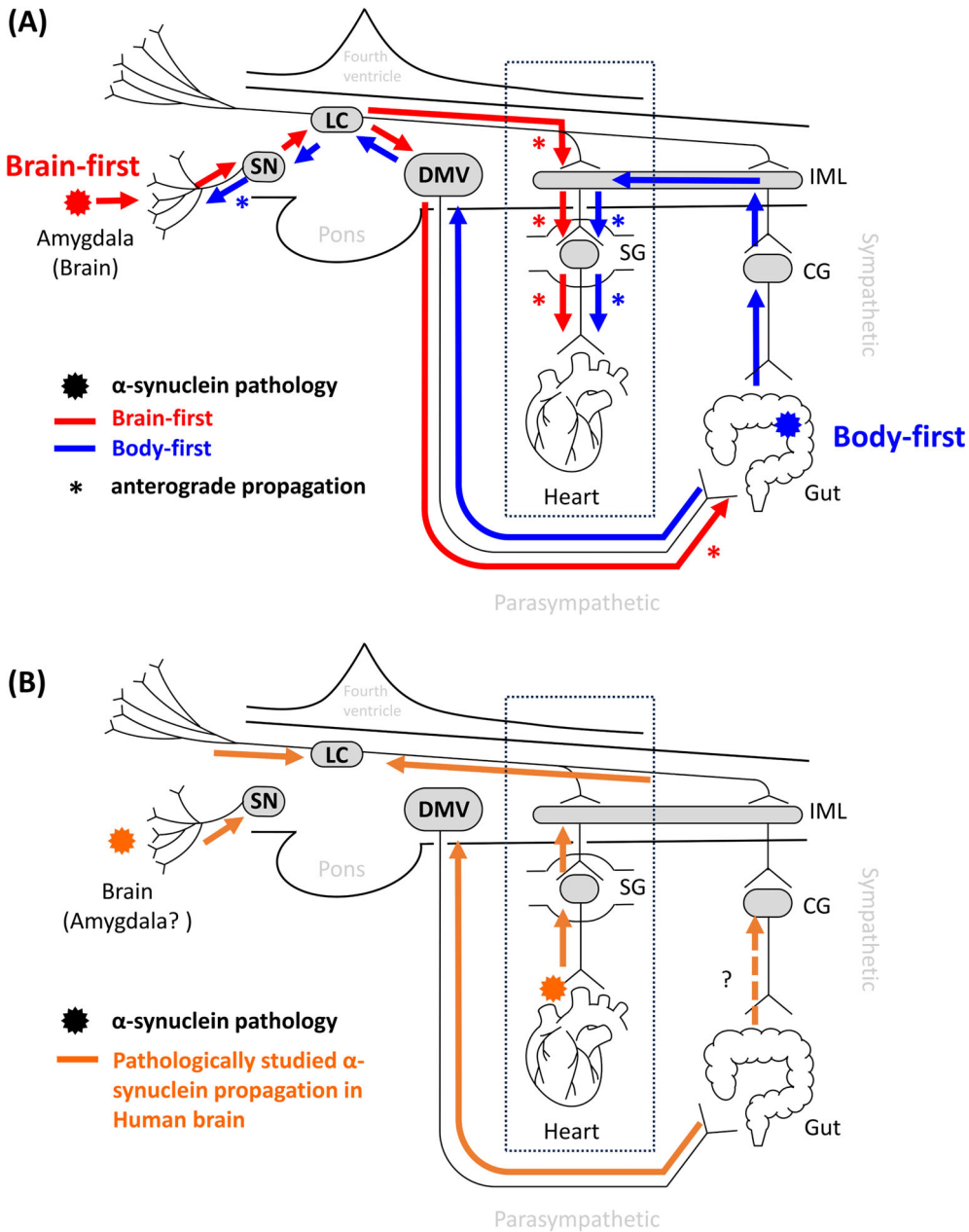

FIG. 1. Propagation route of α-synuclein (aS). aS propagation route proposed in brain-first versus body-first (BVB) hypothesis (**A**) and route suggested from human pathological studies (**B**). The BVB model hypothesizes spread of aS from IML to SG, whereas pathological studies suggest spread from SG to IML. CG, celiac ganglia; DMV, dorsal motor nucleus; IML, intermediolateral nucleus; LC, locus coeruleus; SG, sympathetic ganglia; SN, substantia nigra.

regardless of pathological transmission from other sites. Further, the possibility of hematogenous propagation raises a question about the premise behind the Braak hypothesis and the SOC model, which adopt spatial LB gradients as a guidepost for pathological progression. It is also possible that a spatial LB gradient could be caused by differences in the vulnerability of various nuclei to LB,[20] which is determined by various molecular mechanisms, such as mitochondrial dysfunction, autophagy-lysosome malfunction, and aberrant vesicular transport machinery.[29] In addition, transmission of aS seeds via the cerebrospinal fluid, insufficient clearance of misfolded aS because of glymphatic system dysfunction, and/or *concomitant proteinopathies* (eg, amyloid β, tau, and TDP-43) may also contribute to pathological progression of PD.[30-33]

In brief, it is now becoming clearer that the exclusive idea of explaining all of the PD pathology based solely on neuron-to-neuron transmission of LBs, which is the logical basis of the SOC model, cannot sufficiently explain the actual pathological changes in PD. Therefore, other mechanistic backgrounds, such as multifocal origin of aS

pathology and nonneurogenic transmission, should be considered.

Cardiac Sympathetic Degeneration as a Common and Unique Pathological Event in PD

The notion that cardiac sympathetic nerves are a pathological origin in PD is supported by the results of nuclear imaging studies, which provide further insights into their clinical significance. Postganglionic cardiac sympathetic degeneration can be visualized using ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy. The outcome measures of this imaging include early and delayed heart-to-mediastinum (H/M) ratios of ^{123}I-MIBG uptake on anterior planar images calculated 15–30 minutes and 3–4 hours after radiotracer injection, respectively, and the washout rate (WR), which represents the ratio of changes in cardiac uptake between early and delayed scans, is also assessed.[34] Cardiac MIBG abnormality is a robust marker of LBDs, and the finding of an abnormal cardiac MIBG scan is included in the diagnostic criteria for PD and DLB.[35,36] It should be noted that some familial forms of PD, such as PARK-PARKIN and PARK-LRRK2, show pure nigral degeneration without LB pathology and retain cardiac MIBG uptake.[37] In addition, some patients with multiple system atrophy present slight cardiac MIBG abnormalities in association with postganglionic cardiac sympathetic neurodegeneration. In the differential diagnosis of PD, the specificity and sensitivity of MIBG cardiac scintigraphy are >80% and approximately 70%–90%, respectively.[35,36,38,39] A recent clinicopathological validation study demonstrated that the early H/M ratio shows highest specificity to discriminate between LBDs and non-LBDs than the delayed H/M ratio and WR, when using standardized cutoff values.[40]

Despite its high specificity, the diagnostic sensitivity of MIBG cardiac scintigraphy is lower in the early stages than in the late stages of PD.[38] This finding indicates the existence of subgroups in which cardiac sympathetic denervation is observed in advanced stages, but not in early stages. By contrast, some patients present with severe abnormality on MIBG cardiac scintigraphy at the beginning of motor symptoms.[16] These results support the view that cardiac sympathetic denervation can occur independent of dopaminergic neurodegeneration in PD. Based on these notions, we recently conducted a study that developed the biological subtypes of PD according to nuclear imaging biomarkers, including early H/M ratios on MIBG cardiac scintigraphy.[12] We investigated whether PD can be classified into meaningful subtypes based solely on nuclear imaging findings and disease duration without any consideration of clinical findings. As a result, two distinct PD subtypes were identified. One subtype with early severe cardiac denervation was associated with significant cortical atrophy independent of dopaminergic degeneration severity, and it was referred to as the cardio-cortical impairment subtype. The other subtype is characterized by a more significant striatal dopaminergic terminal loss compared with the cardio-cortical impairment subtype but less severe cardiac sympathetic denervation and cortical atrophy even in advanced stages. This was referred to as the dopaminergic-dominant dysfunction subtype. Our method aimed to classify patients with PD based on dopaminergic and extradopaminergic denervation severity, which indicates that the PD subtype classification was based on the distribution of aS pathology. In contrast, the brain-first versus body-first PD hypothesis does not accurately reflect the pathologically relevant classification of PD. Theoretically, LB pathology has not reached below the brainstem at the de novo stage of the brain-first PD subtype. However, in the study of Horsager et al,[16] nearly half of the patients with the brain-first PD subtype exhibited severe cardiac denervation even at the de novo PD stage, which clearly contradicts their hypothesis.

Furthermore, recent studies on RBD have also cast doubt on the brain-first versus body-first PD hypothesis. Idiopathic RBD (iRBD) is considered a prodromal stage of the body-first PD subtype,[41-43] and a caudorostral gradient of imaging abnormality is interpreted as corroborating evidence for body-to-brain progression. Indeed, iRBD frequently shows autonomic dysfunction along with reduced cardiac MIBG uptake, a marker for body involvement. However, recent studies have shown that patients with iRBD are often accompanied by olfactory dysfunction and cognitive impairment, indicating higher cortical involvement.[41,44] These findings suggest that patients with iRBD may have dysfunction in broader brain regions beyond focal brainstem lesions, arousing further suspicion of the brain-first versus body-first hypothesis.

Taken together, these arguments suggest that the brain-first versus body-first hypothesis does not accurately reflect the pathologically relevant classification of PD.[16] In contrast, the notion that cardiac sympathetic nerves can be an independent initiation site of the aS pathology in PD ensures a better understanding of the pathogenesis and subtype classification of PD. This view may also improve clinical trial designs and contribute to the development of disease-modifying therapies.

Conclusion

The attempt to explain the pathological changes in PD in terms of inter-neuronal transmission of aS misfolding has attracted significant attention. Further, it has provided an understanding of the pathophysiological background

of PD. However, it has become evident that this oversimplified concept does not explain the complexity of actual PD pathology, particularly when considering involvement of the cardiac sympathetic nervous system. Other conceptual models, such as multifocal and/or diffuse onset and nonneurogenic transmission of protein misfolding, could also be considered promising hypotheses that address the heart of the matter in PD. ■

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Data Availability Statement

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

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