The Gut and Parkinson’s Disease—A Bidirectional Pathway

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Humans evolved a symbiotic relationship with their gut microbiome, a complex microbial community composed of bacteria, archaea, protists, and viruses, including bacteriophages. The enteric nervous system (ENS) is a gateway for the bidirectional communication between the brain and the gut, mostly through the vagus nerve (VN). Environmental exposure plays a pivotal role in both the composition and functionality of the gut microbiome and may contribute to susceptibility to neurodegenerative disorders, such as Parkinson’s disease (PD). The neuropathological hallmark of PD is the widespread appearance of alpha-synuclein aggregates in both the central and peripheral nervous systems, including the ENS. Many studies suggest that gut toxins can induce the formation of α-syn aggregates in the ENS, which may then be transmitted in a prion-like manner to the CNS through the VN. PD is strongly associated with aging and its negative effects on homeostatic mechanisms protecting from inflammation, oxidative stress, and protein malfunction. In this mini-review, we revisit some landmark discoveries in the field of Parkinson’s research and focus on the gut-brain axis. In the process, we highlight evidence showing gut-associated dysbiosis and related microbial-derived components as important players and risk factors for PD. Therefore, the gut microbiome emerges as a potential target for protective measures aiming to prevent PD onset.

Keywords: Parkinson’s disease, enteric nervous system, microbiome, neurotoxicants, probiotics

INTRODUCTION

Parkinson’s Disease (PD) is a common neurodegenerative disorder typically associated with the progressive loss of dopaminergic neurons located in the midbrain nucleus substantia nigra pars compacta (SNpc) (1). Although the cardinal symptoms of PD are motor impairments attributed to the depletion of the neurotransmitter dopamine in the striatum, a major target of the SNpc (2), it has been long recognized [for review, see (3)] that other non-motor symptoms, including olfactory (4–6) and gastrointestinal (GI) dysfunction (4), appear during the so-called premotor phase of the disease.

The neuropathological hallmark of PD is the presence of cytoplasmic inclusions, called Lewy bodies (LB) or Lewy neurites (7–9), in SNpc neurons (10). LBs are composed mostly of α-synuclein (α-syn) aggregates (11–13), whose aberrant soluble oligomeric conformations are thought to mediate its toxic effects (14). Alpha-syn is an intrinsically disordered protein (IDP), which lacks a stable 3D structure under physiological conditions and is characterized by exacerbated structural plasticity and conformational adaptability (15). As other IDPs possessing amyloidogenic
regions (16), α-syn can turn into a promiscuous binder leading to abnormal interactions and the development of PD (17). Tuttle et al. (18) provided a detailed 3D structure of functional α-syn fibrils (see Figure 1), using solid-state NMR spectroscopy. The study may serve as the basis for a better understanding of molecular mechanisms involved in α-syn fibril nucleation and propagation. In addition, such structural information may provide useful insights on possible interactions of α-synuclein with other proteins and small molecules and allow the emergence of new tools with potential to facilitate both the diagnosis and treatment of PD (e.g., imaging agents and therapeutic drugs).

Aggregates of α-syn fibrils are also found in neural tissue located outside the central nervous system (CNS) of PD patients, in both the autonomic and enteric nervous system (ENS), an outcome which may be associated with the non-motor symptoms of the disease [for review, see (3)]. These findings led Braak et al. (4) to propose a staging system for the progression of the disease following a specific pattern of α-syn aggregates spreading from peripheral toward more centralized locations in the brain. The triggering event would be the invasion of vulnerable neural structures such as the olfactory epithelium and the ENS, which interface directly with the external environment (5, 22), by a neurotoxicant (“neurotropic virus”) (23). While both structures (24, 25) possess immunological and physical barriers protecting them against environmental insults, these barriers steadily deteriorate with aging [for review, see (26, 27)], which is the biggest risk factor for idiopathic PD (28).

Animal studies have supported the claim that α-syn aggregates propagate in a prion-like manner ([29]; for review, see (30)] via microtubule-associated transport along axons (31). In summary, the prion hypothesis of PD proposes that amyloidogenic α-syn would induce a conformational change in the endogenous protein through permissive templating, convert it into a likeness of itself (32, 33) and propagate retrogradely through the vagus nerve or the olfactory tract from the ENS or the olfactory bulb, respectively. Even though definitive proof for this prion hypothesis is still missing (30) and there is the controversial possibility that intestinal α-syn aggregates have a brain origin (34, 35), it has been shown that vagotomy is associated with a decreased risk for PD in humans (36, 37). Also, grafted neurons in PD patients develop α-syn aggregate pathology (38–40) and α-syn from PD patients can cause nigrostriatal degeneration in mice and non-human primates (41). Remarkably, exogenous α-syn fibrils, either PD patient-derived or produced in E. coli, were able to seed the formation of LB-like inclusions which spread from the GI tract to the brain through the vagus nerve in rats (31).

Prior to Braak’s hypothesis, however, there was already strong evidence pointing to the role played by exogenous toxins in the etiology of sporadic PD. For instance, postencephalitic parkinsonism (von Economo’s disease), which has an autoimmune basis caused by a viral illness (42), is associated with degeneration of the basal ganglia (43). Additionally, the discovery of parkinsonism induced by 1-methyl-4-phenyl-1,2,4,5-tetrahydropyridine (MPTP) through self-administration, in 1982 (44) brought to light a new class of xenobiotic substances that may cause PD-like symptoms by environmental contact. MPTP is a lipophilic compound which readily passes into the brain where it is converted by monoamine oxidase B (MAO-B) to 1-methyl-4-phenylpyridinium (MPP+) (45) which is taken up by dopaminergic cells and impairs mitochondria respiration by poisoning complex I (46). There are many heterocyclic molecules that structurally resemble MPTP and are found in the brain from both endogenous and exogenous sources, such as tetrahydroisoquinolines (TIQ) and β-carbolines (β-C). For instance, a TIQ derivative, salsolinol, which is produced by enterobacteria (47) and has been found in the urine of PD patients, may have a double-faced, dose-dependent effect on the nigrostriatal pathway as either a harmful or protective agent (48).

The evidence for the role played by toxins in inducing parkinsonism and the relative scarcity of familial cases (about 10%) (49) underscores the importance of environmental and lifestyle factors over genetic ones in the etiology of the disease (50–52). Some chronic diseases have been associated with a phenomenon called evolutionary mismatch when ancestral traits are no longer adaptive in modern contexts (53, 54). For instance, α-syn is involved with normal synaptic function by regulating, among other things, the size of presynaptic vesicles (55) and the assembly of SNARE proteins involved with the docking of synaptic vesicles to presynaptic membranes (56). However, as old age became common in humans after the early upper Paleolithic (57), the steady increase in longevity seen in modern times may have had a collateral effect on the protein homeostasis (proteostasis) network, which coordinates protein synthesis, folding, trafficking, disaggregation, and degradation (58, 59). The breakdown of proteostasis, which is a common feature of many neurodegenerative diseases (60), means that misfolded proteins may accumulate due to lack of clearance or failure to refold into their native structures (61). In the case of prion-like proteins, this may cause further protein misfolding (template effect) leading to protein aggregation and ultimately cell death (62).

THE GUT-BRAIN AXIS AND PARKINSON’S DISEASE

The gut-brain axis is mediated by intense bidirectional communication between the CNS and the ENS (63). Through the ENS, the gut microbiota influences the development and function of all divisions of the nervous system (64) and this association was established very early during the evolution of multicellular organisms. The first nervous system appeared more than 500 million years ago before the divergence of cnidarians and bilaterians, the two metazoan sister groups (65). That primitive brain had a simple structure, organized as a diffuse nerve net which controlled a restricted set of basic behaviors and was the template for the subsequent evolution of the mammalian ENS (66–68), which retained many of its basic structural characteristics, such as a network of nervous ganglia distributed in the myenteric and submucous plexuses (69). Higher vertebrates went to evolve an additional set of neural structures in the central nervous system (CNS), tasked with the control of more sophisticated behaviors (70). However, the ENS and the CNS maintain intense crosstalk through reciprocal connections mediated by the VN (Figure 1) and pelvic nerve in mammals.
FIGURE 1 | The gut epithelium is a multifunctional interface. The bidirectional interplay between the brain and the gut is mediated by neural, such as the vagus nerve (VN-gateway), and humoral pathways, such as the lymphatic tissue and the bloodstream (Non-VN gateways). A monolayer of epithelial cells separates the intestinal lumen and the complex gut microbiome from the underlying lymphoid and enteric nervous tissues. The structure of alpha-synuclein amyloid fibrils (PDB 2N0A) is based on atomic-resolution molecular data from NGL Viewer (19). Members of the gut microbiome and their extracellular compounds may trigger responses in the VN through enteroendocrine cells, which are contacted by vagus nerve terminals through specialized structures called neuropods (NP) (20). Microbial antigens can cross the gut epithelium through microfold cells, playing a central role in localized inflammatory responses [adapted from Bohórquez et al. (21)]. Toll-like receptors are microbe-sensing proteins, present in intestinal epithelial cells, mediating recognition of commensal bacteria from the harmful/inflammatory ones. ENS, enteric nervous system; M, microfold cells; NP, neuropods; PP, Peyer’s patches; TLR4, Toll-like receptor 4; VN, vagus nerve.

THE GUT MICROBIOME AND BRAIN FUNCTION

There is increasing evidence of the association between microbiome dysfunction and CNS-related co-morbidities, such as anxiety, depression, autism spectrum disorders, Alzheimer’s disease and PD (88–92). This association probably arose as a by-product of natural selection forces acting on microorganisms to adapt to the host and vice-versa (93). The effect of the microbiota on the CNS can lead to behavior modifications (93–95) and even to host manipulation (96) associated with increasing fitness of its bacterial populations. For instance, the microbiome can influence social interactions by acting on the nutritional behavior of individual animals, particularly those from social species where individuals share microbes and interact around foods (97). The proximate neuro-endocrinological and inflammatory mechanisms underlying this type of host manipulation are largely shared by the microbiome and the host (98, 99). For instance, levels of many neurotransmitters that are important for the expression of social behavior, such as serotonin (5-HT), dopamine, norepinephrine (NE), γ-aminobutyric acid (GABA), and glutamate are either expressed or regulated by bacteria (100–102). Particularly, most of the body’s serotonin (5-HT) (5-hydroxytryptamine) is produced in the gut by enterochromaffin cells (EC) under the influence...
of the microbiome (103). The activation of 5-HT<sub>4</sub> receptors induces the maturation of the ENS and regulates its adult function (104). In the gut, there are three major metabolic pathways leading from the essential amino acid tryptophan (Trp) to 5-HT, kynurenine (Kyn), and indole derivatives, which are under the direct or indirect control of the microbiota (105). During inflammatory states, most tryptophan is diverted to the production of Kyn and its metabolites kynurenine acid (KYNA) and quinolinic acid (QUIN) (106). While KYNA is considered neuroprotective, QUIN can cause excitotoxicity and contribute to the neuropathogenesis of PD [for review, see (107)].

Although α-syn aggregates are also seen in the ENS of normally aging subjects (108), especially in the appendix (109), it is more prevalent in PD patients (110). Recent in vivo models showed that accumulation of α-syn aggregates in the ENS can be induced by alterations in the gut microbiome (111). Interestingly, Sampson et al. (112) demonstrated in mice, genetically modified to overexpress α-syn, that the presence of gut microbiota is necessary to promote pathological alterations and motor deficits similar to PD. They also demonstrated that fecal transplants from PD patients impair motor function in the same mouse strain, strongly suggesting that gut microbes may play a pivotal role in the onset of synucleinopathies such as PD (112). Underlying these findings is the fact that microbial amyloids produced by some members of the gut microbiota can be released in the extracellular space, where they can be internalized by neighboring cells, including neurons, and seed the formation of pathological aggregates of endogenous α-syn through permissive templating (113, 114). The failure of normal clearance mechanisms such as the ubiquitin-proteasome system, characteristic of both familial and idiopathic PD (115), to degrade the misfolded protein, may facilitate the seeding process.

The concept of microbial dysbiosis also comprises the bacteriophage components of the microbiome (116). Bacteriophages (phages) are viral parasites of bacteria and are important regulators of host-microbiome interactions through horizontal gene transfer and antagonistic coevolution (117, 118). Besides targeting bacteria, phages can impact human health by playing a direct role on intestinal inflammatory processes (119) and possibly causing α-syn misfolding (120). A recent study showed significant differences in the gut phagobiota of PD patients and healthy individuals and a depletion of Lactobacillus bacteria (121) in the former, which is associated with the regulation of gut permeability (122) and dopamine production (102), two factors linked with the early signs of PD in the gut (123). Phage therapy has recently returned to the spotlight as an alternative antimicrobial strategy (124, 125). Eventually, it may also contribute to fighting PD through targeted approaches to manipulate the microbiome (121).

Probiotic bacteria have been linked to improved GI symptoms associated with PD (126). Probiotics affect the functionality of the CNS through beneficial interactions with the commensal gut microbiota and modulation of gut-derived inflammation (127). The microbiota of PD patients exhibits a pro-inflammatory profile (128, 129) due to increased intestinal permeability to endotoxins (lipopolysaccharide) (130). Bacterial amyloids may also favor a pro-inflammatory environment in the gut (131). A common bacterial component, the Curli amyloids, share structural and biophysical properties with amyloids and are produced by E. coli through coordinated biosynthetic processes (132). Other components of the gut microbiome are also known to produce functional extracellular amyloids [e.g., Salmonella, Klebsiella, Citrobacter, and Bacillus species; (133)]. Since probiotic treatment induces an anti-inflammatory peripheral immune response in multiple sclerosis patients (134) there is a possibility they may also be beneficial for PD patients, although there are no reports corroborating this hypothesis. One option is to take advantage of Lactobacilli’s ability to inhibit the formation of biofilms by pathogenic bacteria (135, 136). One caveat, however, is that the effects of probiotics are highly variable, being person-specific, as shown in a recent study (137). This limitation may be counteracted with the use of genetically-modified probiotics able to deliver novel therapeutics efficiently and with site specificity (138). Despite the increasing number of probiotic products available to consumers and the aggressive marketing proclaiming their efficacy, there have been few studies addressing concerns about efficacy and, more importantly, the safety of these products (139). There is an urgent need for more studies about the therapeutic potential of specific bacterial strains to help maintain oxidative and protein homeostasis in the ENS.

**CONCLUDING REMARKS**

Aging is the main risk factor for the development of PD (140) and delaying the aging process is neuroprotective to PD in animal models (141). Aging is also associated with the accumulation of neuroinflammatory sequelae and the breakdown of homeostatic mechanisms that protect against protein misfolding, oxidative stress, decreased mitochondrial function, etc. The gut, as one of the main gateways to environmental exposure to the brain, may contribute to increasing the susceptibility to these factors. The microbiome has a protective effect mitigating this exposure, and dysbiosis seems to be a pivotal risk factor for PD and other neurological disorders. Thus, the adoption of preventive measures to ensure a healthy microbiome throughout the lifetime can potentially decrease the risk of developing PD and other neurodegenerative diseases. The widespread use of antibiotics, for instance, which can kill gut bacteria indiscriminately, can cause a shift of the microbiome to an alternative stable state with unknown consequences in the long term (142).

**AUTHOR CONTRIBUTIONS**

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.
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