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Enteric nervous system manifestations of neurodegenerative disease

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Abstract

Neurological disorders cause gastrointestinal (GI) symptoms that are debilitating and markedly diminish quality of life in patients. The enteric nervous system (ENS), the intrinsic nervous system of the GI tract that is often referred to as “the second brain”, shares many features with the central nervous system. The ENS plays an essential role in regulating many GI functions including motility and fluid secretion. Enteric neuronal degeneration could therefore be responsible for the GI symptoms commonly observed in neurological conditions. Here we describe the organization and functions of the ENS and then review the evidence for ENS involvement in two common neurodegenerative disorders, Parkinson’s disease (PD) and Alzheimer’s disease (AD). Data from patients as well as animal models suggest that PD affects distinct subsets of neurons and glia in the ENS, and that the ENS may participate in the pathogenesis of this disorder. While there has been great enthusiasm for the possibility of sampling the ENS for diagnosis or therapeutic monitoring of PD, further work is needed to determine which enteric neurons are most affected and how ENS function could be modulated to ameliorate GI symptoms in patients. Although AD is far more common than PD and AD patients also experience GI symptoms, understanding of ENS dysfunction in AD is in its infancy. Much work remains to be done in both of these fields to determine how the ENS contributes to and/or is altered by these disorders, and how to target the ENS for more effective treatment of GI comorbidities.

Keywords

Enteric nervous system; Parkinson’s disease; Alzheimer’s disease; Neurodegeneration

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Introduction

The enteric nervous system (ENS) is often referred to as the “second brain” in the bowel because it shares many features with the brain, including the full complement of neurotransmitters utilized for synaptic transmission, ultrastructural features of neuron-glia interactions, similar transcriptional programs for generating neuronal diversity, and a laminar organization[1]. The ENS is in fact the largest division of the peripheral nervous system (PNS) and is unique in the PNS because it can perform many of its functions independent of input from the central nervous system (CNS). The ENS consists of two ganglionated plexuses composed of neurons and glia that regulate a variety of gastrointestinal functions and are essential for life (Figure 1A). A more detailed description of the structure, function and component cell types of the ENS is beyond the scope of this review, but has been well reviewed in the past[2, 3]. While the ENS does not require CNS input to perform its duties, in practice, it works in collaboration with vagal, sympathetic and parasympathetic inputs to regulate many GI functions, such as motility. This bi-directional communication between the ENS and other parts of the nervous system has been postulated to serve as a conduit for transmission of pathogenic proteins and infectious particles, such as α-synuclein and prions, from the gut to the brain. Another article in this special issue addresses the latest evidence in support of this possibility, often referred to as Braak’s hypothesis[4]. Not only is the ENS a potential portal for the pathogenesis of neurodegenerative disorders, there is growing evidence that the ENS is also a target of these disorders. ENS dysfunction can be associated with a number of GI symptoms including severe constipation, anorexia, and delayed gastric emptying (gastroparesis), which are all common in patients with neurodegenerative conditions. This review presents the latest evidence for ENS involvement in two common neurodegenerative disorders, Parkinson’s disease (PD) and Alzheimer’s disease (AD), and discusses the need for sampling the ENS for disease monitoring and therapeutic development.

Parkinson’s disease

PD is a chronic, progressive movement disorder characterized by rigidity, resting tremor, postural instability and bradykinesia. While these motor symptoms were defined decades ago, it was only more recently recognized that PD can also affect bowel function, causing constipation that often starts before motor symptoms and correlates with disease severity[5]. In the CNS, PD is associated with toxic accumulation of α-synuclein protein aggregates in cell bodies (Lewy bodies; LB) and neurites (Lewy neurites), leading to degeneration of nigrostriatal dopaminergic neurons. With the advent of antibodies that made it easier to detect α-synuclein accumulation, several groups reported Lewy-type pathology in enteric neurons from biopsies of PD patients, suggesting that the ENS could be involved in PD[6, 7]. A series of subsequent studies have tried to determine whether Lewy pathology in the ENS is specific to PD, pre-dates motor functions, and correlates with PD disease severity (summarized in Table 1)[8–12]. These studies have shown that α-synuclein aggregates can be detected in the ENS more commonly in PD patients than healthy controls, but it remains unclear if this is associated with enteric neurodegeneration or GI symptomatology. In total, Lewy pathology was most often detected in the submucosal plexus and dopaminergic neurons were not necessarily the most affected. A major challenge in conducting and

interpreting these studies is that many aspects of enteric neuronal organization remain unknown and it is not clear if PD targets a specific site or neuronal subtype in the ENS the way it targets the substantia nigra in the CNS. Studies of ENS pathology in PD have thus offered inconsistent findings with regard to which plexus and type(s) of neurons are most affected. These inconsistencies prompted an effort to change the methodology for assessment of Lewy type α-synucleinopathies (LTS) to improve sensitivity and specificity[13]. A consortium of laboratories used a series of defined immunohistochemical methods to detect pathological α-synuclein from full thickness sections of the sigmoid colon at autopsy and found the highest prevalence of pathological LTS staining in neuronal elements of the submucosa[14]. In PD patients with chronic constipation, colonic submucosal neurons downregulate vasoactive intestinal peptide (VIP), but are not lost[15]. These data suggest that constipation in PD could be secondary to dysfunction, but not loss, of VIPergic secretomotor neurons in the submucosal plexus. Larger studies with careful standardization of assays and locations sampled will be required to test this hypothesis.

Enteric neuropathies in animal models of PD

Animal models of PD are based on either pharmacologic or genetic approaches to simulate nigrostriatal neurodegeneration and PD pathogenesis. The first and most commonly used pharmacologic models of PD have been based on administration of one of two neurotoxins to mice, rats, or more recently, nonhuman primates. Both of these neurotoxins, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA), consistently affect the dopaminergic nigrostriatal pathways[16], but their impact on gut function and the ENS is variable, depending on the agent, mode of administration, and assays used (reviewed in Table 2)[17–20]. Systemic MPTP administration in both mice and non-human primates causes loss of dopaminergic neurons in the myenteric plexus, but no major defects in GI motility[17, 18]. Interestingly, delivery of 6-OHDA directly into the substantia nigra is sufficient to slow colonic motility, suggesting that the constipation observed in PD patients could reflect CNS pathology alone[19, 20]. Unfortunately, the submucosal plexus was not analyzed in some of these studies making it difficult to make direct comparisons to the most robust findings from PD patients.

A breakthrough in the understanding of PD pathogenesis was the demonstration that a single intra-striatal injection of synthetic α-synuclein fibrils in a normal mouse was sufficient to transmit the pathologic form of α-synuclein from cell to cell in anatomically connected brain areas[21]. This transmission was accompanied by LB formation, a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), and motor deficits, effectively modeling the progression of PD[21]. Intragastric administration of a third neurotoxin, the pesticide rotenone, recapitulates this cell-to-cell transmission of α-synuclein. Pesticide exposure has been linked to PD in epidemiological studies, and chronic intragastric administration of rotenone causes nigrostriatal degeneration preceded by LTS and myenteric neuron loss in mice[22–25], suggesting it might be a particularly good rodent model of PD. In rotenone-treated mice, ENS neurodegeneration was associated with slowed GI motility prior to onset of CNS findings, suggesting that in addition to serving as a portal for α-synuclein transmission to the CNS, ENS Lewy pathology could be sufficient to explain the GI symptoms in early PD[24].

Genetic models in which transgenic mice over-express either the wildtype or the human mutant forms (A53T or A30P) of theα-synuclein gene have also been used to study PD α-synucleinopathies26. In most of these mouse models, age-dependent aggregation of α-synuclein in either enteric neurons or varicosities around enteric neurons is associated with GI motility dysfunction, particularly slowed colonic transit (Table 2)[27–30]. In a subset of these models, moreover, pathological aggregation of α-synuclein was shown to both spread from the dorsal motor nucleus of the vagus (DMV) to the ENS via vagal efferent fibers in A53T transgenic mice[30], or from the ENS back to the DMV via retrograde transport when human αsynuclein pre-formed fibrils were injected into the wall of the intestine31. Genetic and chemical injury models of PD both support the idea that enteric neurons are vulnerable to α-synucleinopathies.

Relative vulnerability of nigrostriatal and enteric neurons

The diverse risk factors that determine the vulnerability of specific types of neurons in neurodegenerative disorders, such as nigrostriatal dopaminergic neurons in PD, are still being defined[32, 33]. Nigrostriatal dopaminergic neurons exhibit sustained depolarizing activity patterns that could lead to metabolic stress and mitochondrial dysfunction[34, 35]. Other suggested risk factors are autonomous activity, limited calcium buffering capability, and long, poorly myelinated axons[35]. Many enteric neurons, particularly those involved in peristalsis, are autonomous and probably continuously active, making them similarly vulnerable. Guinea-pig myenteric ganglia in organotypic explants exposed to rotenone or sustained high K^+ induced depolarization for several days, form and accumulate α-synuclein fibrils in axonal varicosities of cholinergic neurons[36]. Enteric neurons all have unmyelinated axons and many have multiple synaptic endings, features that could also increase their vulnerability in PD and could facilitate the release and reuptake of α-synuclein and its propagation through connected ganglia (Figure 1B). Consistent with this, cultured embryonic enteric neurons accumulate α-synuclein when treated with forskolin, and release it upon depolarization[37]. Enteric neurons also have unique vulnerabilities related to their close proximity to the intestinal epithelium and gut mucosal immune system, both of which can become altered in PD and potentially harm enteric neurons[38, 39]. Further exploration of which subsets of enteric neurons are most affected in PD will help define the characteristics that place them at risk and advance the development of enteric neuroprotective therapies.

Alzheimer’s disease

AD is a neurodegenerative disorder causing progressive cognitive impairment and loss of working memory. Brain pathology is characterized by extracellular plaques containing β-amyloid (Aβ) and intracellular neurofibrillary tangles comprised of hyper-phosphorylated tau protein. AD, like many neurological disorders, is associated with a variety of GI symptoms, raising the possibility that the ENS could also be affected. Supporting this idea, an early report showed that plaques immunoreactive for Aβ could be found in the submucosa of two AD patients[40]. Amyloid precursor protein (APP), from which Aβ is derived, is normally expressed by enteric neurons and glia[41], making it further plausible that AD pathophysiology could involve the ENS. Follow up studies, however, have been limited in number and shown conflicting results. A study of autopsy specimens from esophagus,

stomach, small and large intestine from 18 AD patients found that there was no difference in neuronal density or tau pathology between AD patients and elderly controls, or between AD patients and those with non-AD dementias[42]. Another study reported elevated Aβ immunoreactivity in the colons of 11 patients with AD, but did not include controls[43]. Further studies of enteric neuronal pathology in AD are clearly needed.

While data from human samples is sparse, translational studies have shown that mutations associated with familial AD in human patients can cause GI pathology in mice. In AβPP/PS1 transgenic mice, the mouse prion protein (PrP) promoter directs expression of mutant forms of mouse APP and human presenilin 1, which act to alter APP processing and lead to brain Aβ deposition[44]. Enteric neurons in both plexuses of AβPP/PS1 mice accumulate Aβ but there is no resulting dysmotility or change in overall neuronal density[43, 45]. Gut macrophage density and levels of several pro-inflammatory proteins, however, were markedly increased suggesting that enteric Aβ deposition is not benign. Related mouse models in which either the hamster PrP or Thy1 promoters are used to drive mutant forms of APP within neurons also show amyloid deposits in the bowel, but have divergent effects on neuronal density[46, 47]. A limitation of these studies is that the methods used to measure neuronal density vary and the promoters used to drive transgene expression have often not been fully characterized in the bowel. Regardless, work to date suggests that the Aβ deposits can form in the bowel and trigger an inflammatory response associated with macrophage recruitment. Given the increasing evidence that microglia, the resident macrophages of the CNS, play an important role in the synapse loss associated with AD[48], further investigation of neuroimmune interactions and synaptic deficits in the bowel is warranted.

Conclusions and Future Directions

Given the many commonalities between the CNS and ENS, it is highly likely that disorders that affect CNS function also affect ENS function and that ENS dysfunction contributes to the GI symptoms experienced by patients with neurodegenerative disease. Studies of ENS pathology in PD and AD patients, however, remain limited and often convey conflicting results. Data from animal models is more robust and suggest that ENS involvement in both of these conditions is highly plausible. Enteric ganglia are heterogeneous and it remains unknown to what extent there might be regional specialization or functional “nuclei” along the length of the bowel. To better translate findings from animal models to human disease, it will be important for future studies to carefully standardize the bowel locations sampled and maximize the number of neurons examined from each patient. The submucosal plexus is likely to be of highest yield for further analysis in PD, and therapeutic strategies to protect enteric neurons in the pre-motor phase of PD may be disease modifying, at least for ameliorating GI symptoms. Glial dysfunction is increasingly recognized to play a major role in CNS neurodegeneration but has been little examined in the ENS. Enteric glial involvement in PD and AD remains another important area for future investigation. The GI tract represents a major interface with the outside environment; it is essential to better understand how the neurons and glia embedded within it might serve as conduits for and targets of neurodegenerative disorders.

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HIGHLIGHTS

- The ENS and CNS have comparable neuronal diversity and developmental programs.
- In PD, α-synuclein accumulates in enteric neurons, prior to motor symptoms.
- Genetic and chemical injury models of PD variably affect the ENS
- Submucosal enteric neurons are probably most vulnerable to degeneration in PD
- ENS pathology in AD is understudied; Aβ plaques have been observed in the bowel.

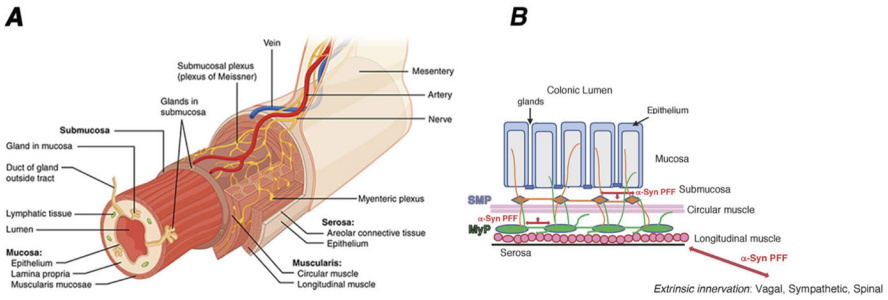

FIGURE 1. Organization of the enteric nervous system and potential pathways for α-synuclein propagation

A: Schematic illustrating the laminar organization of the bowel in three-dimensions from the mesentery to the lumen. The two major plexuses of the ENS are the myenteric plexus (MyP), located in between the circular and longitudinal muscle layers in the muscularis externa, and the submucosal plexus (SMP), located in the submucosa. Image obtained from Wikimedia and reproduced under the Creative Commons Attribution-Share Alike 3.0 Unported license.

B: Schematic of a cross-section of the colon illustrating the interconnected enteric plexuses (MyP and SMP), which are both unmyelinated and contain neurons projecting to the mucosa. Alpha-synucleopathies (α-Syn preformed fibrils [PFF], red arrows) could propagate from pre-synaptic nerve terminals to vulnerable post-synaptic neurons both within the ENS, and from the ENS to the CNS through extrinsic projections to the gut, which include vagal, sympathetic and spinal afferent fibers. This could be one of the factors in the progression of Parkinson's disease.

TABLE 1
Pathological studies of the ENS in human patients with PD

Summary of the studies to date of ENS pathology in human PD. In the CNS column, the clinical diagnosis of the patients studied, presence of motor symptoms, and the sample size is summarized. In the ENS column, the neuropathological marker(s), plexuses examined, and the primary observations of each study are summarized. MyP: myenteric plexus; SMP: submucosal plexus; IR: immunoreactive; DBH: dopamine beta hydroxylase; LB: Lewy Bodies; LN: Lewy neurites; NF: neurofilament; NO: nitric oxide; α-SYN: alpha-synuclein; TH: tyrosine hydroxylase; VIP: vasoactive intestinal peptide; Nd: not determined.

CNS	ENS			
Motor symptoms? (# of patients)	**Affected neuron types, αSYN-IR fibers**	**Neuropathy marker**	**GI symptoms**	**References**
PD, yes (1)	MyP: colon	LBs	Acquired megacolon	Kupsky et al., 1987
PD, yes (10)	VIP-IR elements MyP: esophagus, entire GI tract SMP: duodenum, colon No cell body loss	LBs	Achalasia	Wakabayashi et al., 1988, 1990
Advanced PD, yes (11)	VIP-IR, TH-IR MyP: colon Loss of dopamine-IR neurons and dopamine depletion	LBs	Chronic constipation, megacolon	Singaram et al., 1995
PD, no (5)	Neurofibrillary lesions SMP more affected than MyP in stomach	αSYN-IR inclusions	Not indicated	Braak et al., 2006
Early, mid- and late stages PD; some with motor symptoms (29)	SMP: colon Loss of NF-IR neurons Nerve fibers-IR	LB and LN αSYN-IR	Chronic constipation	Lebouvier et al., 2010
PD, no (9)	SMP: colon Nerve fibers-IR	αSYN-IR	Not indicated	Shannon et al., 2012
PD, no (129)	Plexus unspecified Nerve fibers-IR	No correlation with rostral-caudal gradient of αSYN	Defecatory dysfunction	Cersosimo, Benarroch 2012 Cersosimo et al., 2013
Advanced PD, Yes (7)	Myp: no loss of NO-, VIP-, TH-neurons Nerve fibers-IR in stomach (MyP> SMP) TH-IR rare	αSYN	GI dysfunction unspecified	Annerino et al.,2012
PD, yes (35)	SMP: colon No loss of TH- or DBH- IR neurons	Nd	GI dysfunction unspecified	Corbillé et al., 2014
PD, yes (5)	Sigmoid Colon, full thickness SMP>Muscularis>Mucosa neuronal -IR structures	αSYN/LTS	GI dysfunction	Beach et al., 2016

TABLE 2

Comparative analysis of CNS and ENS manifestations in animal models of PD

Summary of the studies to date on ENS pathology and GI phenotypes in animal models of PD. In the CNS column, the model organism, experimental paradigm (chemical or genetic lesion), and CNS pathology are summarized. In the ENS column, the neuropathological marker(s), plexuses examined, gastrointestinal (GI) deficits and the primary observations of each study are summarized. MyP: myenteric plexus; SMP: submucosal plexus; IR: immunoreactive; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; I.P.: intraperitoneal; I.V.: intravenous; S.Q.: subcutaneous; 6-OHDA: 6-hydroxydopamine; LB: Lewy Bodies; LN: Lewy neurites; α-SYN: alpha-synuclein; NO: nitric oxide; ChAT: choline acetyltransferase; GE: gastric emptying; TGTT: total GI transit time; DAT: dopamine transporter; SN: substantia nigra; TH: tyrosine hydroxylase; nNOS: neuronal nitric oxide synthase; AR: adrenergic receptor; VIP: vasoactive intestinal peptide; DMV: dorsal motor nucleus of the vagus; IML: intermediolateral column of the spinal cord; Nd: not determined

CNS			**ENS**		
PD Model **Route of toxin administration**	**Motor Symptoms (no, yes)** **Affected neurons**	**Affected Neuron types, αSYN-IR fibers plexuses**	**Neuropathy marker**	**GI Symptoms**	**References**
MPTP mice I.P., test after 10 days	Nd	Loss of TH-neurons and NADPH/NO; ChAT unchanged MyP: Ileum SMP: Nd	Nd	Colonic motility transiently increased; GE, TGTT unchanged	Anderson et al., 2007
MPTP rhesus monkeys I.V., test after 5 months	Yes, Decrease striatal DAT	% Total neurons: Increased NOS, decreased TH No change ChAT, VIP No change glia MyP, colon Decreased TH SMP, colon	Nd	No change in stool consistency	Chaumette et al., 2009
6-OHDA rats SN injection *(does not reach the ENS)*, test after 4 weeks	Nd Loss of SN TH- neurons	Increased TH-IR, Decreased nNOS-IR ChAT-IR unchanged Downregulation of TH & nNOS mRNA, ChAT mRNA expression Stomach, colon Plexuses unspecified	Nd	Slower colon motility GE delayed	Zhu et al., 2012
6-OHDA rats SN injected, test after 6 weeks	Yes, (less time Rotarod test) Loss of SN TH-neurons	DA content increased (muscularis exerna), β3-AR upregulated 5-HT4R downregul. colon, plexuses unspecified	Nd	Decreased colonic motility	Zhang et al., 2015
Rotenone rats I.P., 5x/week test after 3d, 1 or 6 months	No, No loss of SN- striatal neurons	Loss of neurons MyP, small intestine SMP, Nd	Loss αSYN-IR (3 day post inj.) LBs (6 months post inj.)	Slower GI motility (6 months post inj.)	Drolet et al., 2009

CNS			ENS		
PD Model Route of toxin administration	**Motor Symptoms (no, yes) Affected neurons**	**Affected Neuron types, αSYN-IR fibers plexuses**	**Neuropathy marker**	**GI Symptoms**	**References**
Rotenone rats Osmotic minipumps S.Q. for 22–28 days	No, Grossly normal behavior Unaltered TH protein content in midbrain or striatum	%total neurons ChAT, NOS, VIP, TH unchanged MyP, Ileum, pylori, proximal colon	Nd	Delayed GE; transient decrease in colonic motility; physiological defect of inhibitory neurons	Greene et al., 2009
Rotenone mice Intragastric, 5d/week for 1.5 or 3 months	No, (rotarod test 1.5 mth) Yes, 3 mth αSYN-IR neurons in SN, dmX, IML, Loss TH-IR, SN	ENS Ganglia , Extra and intra neuronal α-SYN aggreg Gliosis MyP, (Duod ,leum) SMP, Nd	αSYN-IR aggreg (3mth) p-α-SYN	Nd	Pan-Montojo et al., 2010
Mice transgenic for human α-synuclein (expression driven by Thy1 promoter) Aged 8–10 months	No loss of striatal dopamine	αSYN varicoses around pChAT neurons; no loss of pChAT-, nNOS-, TH- or VIP- neurons MyP, distal colon SMP, Nd	αSYN-IR	Normal GE Defecatory dysfunction	Wang et al., 2012
Aged 11–12 months	Nd	Nd	Nd	Slower colonic transit; increased defecation under stress	Wang et al., 2008
Mice transgenic for mutant A53T or A30P human α-synuclein Age: 3–18 months	No dopaminergic deficit, No LB A30P, no gross motor dysfunction A53T, reduced activity, discoordination on Rotarod test	In TH-IR In varicose terminals on NOS-IR MyP and SMP	Mutated αSYN-IR	A53T & A30P Increased GITT. Reduced colonic motility	Kuo et al., 2010
Mice transgenic for mutant A53T inj. stomach LB from brain extract of PD patient Test after 4 months	PD patient presumed motor symptoms	Neurons-IR MyP SMP, Nd	Aggregates Endogenous A53T SYN-IR	Nd	Lee et al., 2011
Mice transgenic for mutant A53T (expression driven by prion promoter) Test 2–20 months	Motor symptoms, Nd DMV efferent fibers A53T SYN- IR	No SYN-IR neurons, only surrounding varicose processes Stomach > Duodenum >colon MyP SMP, Nd	A53T SYN-IR Age related decline	Aged related decline defecation and slower Colonic transit	Noorian et al., 2012