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# Parkinson's disease from the gut

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ABSTRACT

Parkinson's disease (PD) is a debilitating neurodegenerative condition associated with tremor, rigidity, dementia, and gastrointestinal symptoms such as constipation, nausea and vomiting. The pathological hallmarks of PD are Lewy bodies and neurites in the brain and peripheral nerves. The major constituent of Lewy bodies is the neuronal protein α-synuclein. Misfolding of α-synuclein confers prion-like properties enabling its spread from cell to cell. Misfolded α-synuclein also serves as a template and induces misfolding of endogenous α-synuclein in recipient cells leading to the formation of oligomers that progress to fibrils and eventually Lewy bodies. Accumulating evidence suggests that PD may arise in the gut. Clinically, gastrointestinal symptoms often appear in patients before other neurological signs and aggregates of α-synuclein have been found in enteric nerves of PD patients. Importantly, patients undergoing vagotomy have a reduced risk of developing PD. Experimentally, abnormal forms of α-synuclein appear in enteric nerves before they appear in the brain and injection of abnormal α-synuclein into the wall of the intestine spreads to the vagus nerve. Ingested toxins and alterations in gut microbiota can induce α-synuclein aggregation and PD, however, it is not known how PD starts. Recently, it has been shown that sensory cells of the gut known as enteroendocrine cells (EECs) contain α-synuclein and synapse with enteric nerves, thus providing a connection from the gut to the brain. It is possible that abnormal α-synuclein first develops in EECs and spreads to the nervous system.

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## 1. Introduction

Patients with Parkinson's disease (PD) suffer from well recognized motor disturbances including slow movements (bradyskinesia), resting tremor, rigidity, and postural instability. Also common are non-motor symptoms such as loss of smell, sleep disorders and gastrointestinal symptoms, particularly constipation and gastroparesis (Abbott et al., 2001; Cersosimo et al., 2013; Haehner et al., 2009; Iranzo et al., 2006; Jost, 2010). PD is a progressive neurodegenerative disease and is often associated with depression. Interestingly, the non-motor symptoms may precede the manifestation of classic motor disturbances by over a decade (Klingelhoefer and Reichmann, 2015).

The key pathological features of PD are selective degeneration of dopaminergic neurons of the substantia nigra pars compacta and distinctive α-synuclein-containing cytoplasmic inclusions known as Lewy bodies (Angot and Brundin, 2009; Bisaglia et al., 2009; Soto, 2012). Loss of dopaminergic neurons is responsible for the distinctive movement disorder and vagal nerve dysfunction. Alpha-synuclein is the major protein component of Lewy bodies within the soma, axons or dendrites of neurons and is believed to play a pathological role in the progression of PD.

Alpha-synuclein is a 140 amino acid protein that has a propensity to misfold and aggregate (Angot et al., 2012). It is believed that misfolded α-synuclein has the ability to spread from cell-to-cell in a prion-like manner (Desplats et al., 2009; Goedert, 2015; Hansen et al., 2011; Luk et al., 2012; Olanow and Prusiner, 2009). When taken up by another neuron, misfolded α-synuclein can serve as a template for the misfolding of other endogenous α-synuclein molecules (Angot and Brundin, 2009; Goedert, 2015; Steiner et al., 2011) in the recipient cell (Fig. 1). Accumulation of α-synuclein aggregates leads to the formation of oligomers, fibrils, and ultimately Lewy bodies. Although originally described in the brain, aggregated α-synuclein is also found in the peripheral nerves including the enteric nervous system.

Although the ability of misfolded α-synuclein to spread and propagate in a prion-like fashion is well established, it is important to note that it is likely that other regional or cell-autonomous factors are also involved that would account for the regional distribution of PD pathology (Surmeier et al., 2017b). For example, neurons are extremely heterogeneous and those affected in PD are notable for having particularly long and highly branched axons. In addition,

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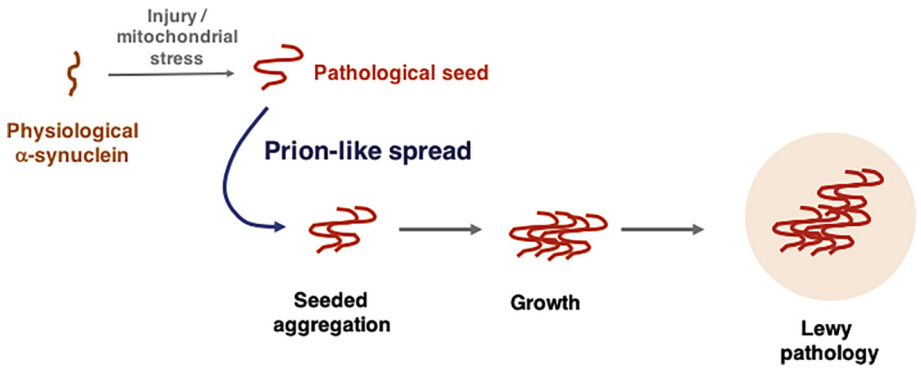


**Fig. 1.** Pathological progression of α-synuclein. Adverse conditions induce changes in the shape of α-synuclein that can serve as a template for misfolding of other molecules. Seeded aggregation leads formation of oligomers and fibrils that comprise Lewy bodies. [()]. Adapted from Goedert, 2015

it appears that dopaminergic neurons of the substantia nigra exhibit particularly high mitochondrial stress and cytosolic calcium levels which promote α-synuclein aggregation(Rcom-H'cheo-Gauthier et al., 2014; Surmeier et al., 2017a). Therefore, the spread of pathogenic α-synuclein together with endogenous factors that render neurons susceptible to damage appear to be responsible for the neurotoxicity seen in Parkinson's disease.

Evidence that Parkinson's disease may originate in the gut has been the topic of several excellent recent reviews (Borghammer, 2017; Lionnet et al., 2017; Surmeier et al., 2017b) and is briefly summarized below. The current article proposes a possible explanation for how PD may originate in the gut in light of the recent unveiling of an enteroendocrine cell – neural circuit and the discovery of α-synuclein in enteroendocrine cells (Bohorquez et al., 2015; Chandra et al., 2017).

## 2. Evidence for PD in the gut

Up to 30% of patients with PD suffer from gastrointestinal symptoms (Pfeiffer, 2003); the most common of which are nausea, vomiting, and constipation (Martinez-Martin, 2011). Although, motility disturbances of the stomach and colon are frequent, any portion of the gastrointestinal tract may be affected (Lang, 2011; Stern and Siderowf, 2010). Interestingly, the onset of constipation usually precedes the motor symptoms of PD (Abbott et al., 2001; Savica et al., 2009) and worsens with disease progression (Edwards et al., 1991). Prolonged colonic transit times have been documented in the disease and are consistent with constipation symptoms (Jost, 2010). Moreover, the development of constipation is independent of age or physical activity (Abbott et al., 2001).

Pathological studies have revealed a chronological and anatomical progression of PD (Braak et al., 1996; Gaspar and Gray, 1984). Identification of neuropathological changes in olfactory neurons and the vagus nerve suggested that PD may spread from peripheral sites before affecting the brain (Braak et al., 2003a,b; Braak and Del Tredici, 2009). Notably, α-synuclein has been shown to be transported in both anterograde and retrograde directions in the vagus nerve (Ulusoy et al., 2013; Ulusoy et al., 2017). Braak and colleagues hypothesized that aberrant α-synuclein accumulation begins in the gut and progresses via the vagus nerve to the brain in a prion-like manner following ingestion of a neurotropic pathogen leading to PD (Del Tredici and Braak, 2008; Hawkes et al., 2009; Reichmann, 2011). Currently, the pathogenesis of PD remains incompletely understood, nevertheless there is considerable evidence that the enteric nervous system is a site of early involvement (Borghammer, 2017; Braak et al., 2003b; Del Tredici et al., 2002). For example, α-synuclein inclusions have been found in submucosal and myenteric neurons (Braak et al., 2003a, 2006; Braak and Del Tredici, 2009) and α-synuclein aggregates seem to appear in enteric nerves before they are found in the brain (Braak et al., 2003b; Braak and Del Tredici, 2009; Corbille et al., 2016a; Hawkes et al., 2010; Pouclet et al., 2012)

Clinical epidemiological evidence supports the concept that PD arises in the gut and spreads to the brain via the vagus nerve. In two studies spanning up to 30 years, it was observed that patients who had a truncal vagotomy (in which the abdominal vagus nerve was transected) but not a highly selective vagotomy (in which only the upper portion of the gastric vagus nerve was transected) had a lower risk of developing PD than the normal population (Liu et al., 2017; Svensson et al., 2015). These studies indicate not only that vagotomy reduces the risk of PD but suggest that the vagus nerve is involved in the transmission of PD and support the concept that PD arises in the gut.

PD is a multifactorial disease with a strong environmental component. Less than 10% of PD is inherited. Environmental exposure to herbicides and pesticides have been associated with an increased risk of PD and high levels of α-synuclein in the brain (Chen et al., 2013; Goldman, 2014; Tanner et al., 2011). The mechanism of toxicity appears to involve inhibition of mitochondrial function or induction of oxidative stress (Tanner et al., 2011). Experimentally, in mice, intragastric administration of the pesticide rotenone, which inhibits mitochondrial complex I activity, induced parkinsonian-like neuropathological changes that were first seen in the enteric nervous system and only later in the substantial nigra pars compacta (Pan-Montojo et al., 2010). Systemic levels of drug were undetectable implying that rotenone induced parkinsonian changes through a local site of action (i.e., the gastrointestinal tract).

In addition to acting locally on the enteric nervous system to mimic PD-like pathology (Pan-Montojo et al., 2010), rotenone's effect on PD-like disease progression was prevented by hemivagotomy or resection of autonomic nerves (Pan-Montojo et al., 2012). Moreover, rotenone caused the release of α-synuclein from enteric neurons where it was taken up by presynaptic neurites and transported in a retrograde fashion to the dorsal motor nucleus of the vagus. These findings indicated that pesticides like rotenone can promote Parkinson's disease progression. This concept was further supported by observing the active transport of α-synuclein from the intestine to the brainstem following injection of monomeric or oligomeric α-synuclein into the intestinal wall in rats (Holmqvist et al., 2014) and are consistent with the early appearance of Lewy bodies in neurons projecting from the vagus nerve in PD (Braak et al., 2003b). Moreover, transport of α-synuclein in a caudo-rostral direction via the vagus nerve has also been demonstrated following direct injection of adeno-associated viral vectors overexpressing human α-synuclein into the vagus nerve (Ulusoy et al., 2013).

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