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The gut-brain axis in Parkinson's disease: Possibilities for food-based therapies

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ABSTRACT

Parkinson's disease (PD) is usually characterized by cardinal motor impairments. However, a range of non-motor symptoms precede the motor-phase and are major determinants for the quality of life. To date, no disease modifying treatment is available for PD patients. The gold standard therapy of levodopa is based on restoring dopaminergic neurotransmission, thereby alleviating motor symptoms, whereas non-motor symptoms remain undertreated. One of the most common non-motor symptoms is gastrointestinal dysfunction usually associated with alpha-synuclein accumulations and low-grade mucosal inflammation in the enteric nervous system. Accumulating evidence suggest that the enteric nervous system is involved in PD pathological progression towards the central nervous system. Moreover, different components of the gut could provide a central role in the gut-brain axis, which is as a bidirectional communicational system between the gastrointestinal tract and central nervous system. Dietary components might influence the gut-brain axis by altering microbiota composition or by affecting neuronal functioning in both the ENS and the CNS. This review gives a comprehensive overview of the evidences supporting the hypothesis that PD could initiate in the gut. We also consider how food-based therapies might then have an impact on PD pathology and/or improve non-motor as well as motor symptoms in PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and is hallmarked by damage to the dopaminergic neurons of the substantia nigra (SN) and by alpha-synuclein containing inclusion bodies (Lewy pathology; LP) in the surviving neurons, resulting in the characteristic motor impairment. It has a prevalence of 0.3% in the general population and 1–3% in the population over the age of 65 (de Rijk et al., 2000; Nussbaum and Ellis, 2003). Although PD is generally considered as a movement disorder, it has long been recognized that the symptoms go beyond motor dysfunction since PD patients very often develop non-motor symptoms, including cognitive impairment (Aarsland et al., 2017), hyposmia (Haehner et al., 2009; Ponsen et al., 2009; Ross et al., 2006), pain (Waseem and Gwinn-Hardy, 2001), depression (Remy et al., 2005), tiredness, orthostatic hypotension (Lim and Lang, 2010) and most commonly, gastrointestinal (GI) dysfunction (Fasano et al., 2015; Jost, 2010; Pfeiffer, 2011; Savica et al., 2009). Some of these symptoms may precede the classical motor symptoms by several years (Abbott et al., 2001; Chen et al., 2015; Gao et al., 2011) and their occurrence in otherwise healthy people has been associated with an increased risk of developing PD (Abbott et al., 2001; Ponsen et al., 2009).

In recent years, special focus has been placed upon the GI tract and the associated enteric nervous system (ENS) in the development of PD (Clairembault et al., 2015; Klingelhoefer and Reichmann, 2015; Mulak and Bonaz, 2015; Pan-Montojo et al., 2012). The ENS is an integrative network of neurons in the GI wall and a major player in the gut-brain axis which is a bidirectional communication system between the central nervous system (CNS) and the GI tract (Cryan and Dinan, 2012). It has been also lately recognized that the gut-brain interactions might be essentially influenced by the gut microbiota (Borre et al., 2014; Grenham et al., 2011; Rhee et al., 2009).

During the first stages of PD, neurons of the ENS and the olfactory bulbs (OB) were found to contain aggregated and phosphorylated alpha-synuclein (Braak et al., 2006; Shannon et al., 2012b). The ENS and OB are gateways to the external environment and new evidence

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suggests that alpha-synuclein deposition in neurons might begin in the ENS and/or in the OB, where a toxin or a pathogen and associated immune/inflammatory responses might start the detrimental process and spread according to a specific pattern, via the vagal nerve and olfactory tract respectively, to the SN and further areas of the CNS (Braak et al., 2003; Hawkes et al., 2009a, 2010; Klingelhoefer and Reichmann, 2015). It is also possible that these inflammatory responses in the gut might signal to specific parts of the brain systemically and through dysfunctional blood brain barrier structures as seen in PD patients (Guan et al., 2013).

Levodopa is the most commonly used drug in the treatment of PD. It suppresses some of the motor symptoms and compensates for dopaminergic cell loss by enhancing dopamine synthesis in the remaining terminals. This therapy has several side effects (Schrag and Quinn, 2000), it does not prevent dopaminergic neuron degeneration, and has no effects on non-motor symptoms (Lee and Koh, 2015). Moreover, PD-associated GI dysfunction contributes to levodopa response fluctuations (Poewe et al., 2010). Thus, there is an urgent need to better understand gut-brain interactions in PD and to develop new therapeutic strategies targeting the gut-brain axis in order to impact PD pathogenesis.

2. Gastrointestinal dysfunction in Parkinson's disease

Non-motor symptoms in PD were already highlighted by James Parkinson in 1817. Nowadays they are well defined but they remain undertreated. An international study showed that 62% of non-motor symptoms are not reported by PD patients due to embarrassment or because patients are unaware that these symptoms are related to PD (Chaudhuri et al., 2010; Chaudhuri and Schapira, 2009). One of the most common non-motor symptoms in PD are GI dysfunction, with a prevalence of 70–80% (Martinez-Martin, 2011). GI symptoms are identified as bloating, drooling, constipation, nausea, delayed gastric emptying and prolonged intestinal transit time (Abbott et al., 2007, 2001; Cersosimo et al., 2013; Chaudhuri and Schapira, 2009; Fasano et al., 2015; Kaye et al., 2006; Pfeiffer, 2011; Sakakibara et al., 2003; Verbaan et al., 2007) and they are major determinants of quality of life (Gallagher et al., 2010; Martinez-Martin, 2011). The occurrence and prevalence of different GI dysfunctions vary among patients and have been extensively reviewed (Fasano et al., 2015). Among them, constipation is the most prominent and it might precede motor symptoms by over a decade (Fasano et al., 2015; Pfeiffer, 2011). The occurrence of constipation before the manifestation of motor symptoms in PD patients was reported to be 87% (Cersosimo et al., 2013). In addition, constipation is assumed to be a harbinger and is associated with an increased risk of developing PD (Kaye et al., 2006; Sakakibara et al., 2003).

The factors responsible for the initiation of the pathophysiological cascade in PD remain unknown. However, it is likely that environmental factors play a key role (Kieburtz and Wunderle, 2013; Wirdefeldt et al., 2011). The early involvement of the GI tract in PD supports the hypothesis that environmental factors could exert its influence on PD development and progression via the gut.

3. Gut pathology

3.1. Alpha-synuclein accumulation in the ENS

Alpha-synuclein is a protein abundantly expressed in the CNS, mainly in the presynaptic terminals. It is thought to be involved in the regulation of neurotransmission and synaptic homeostasis (Burré et al., 2010; Dikiy and Eliezer, 2012). A pathological characteristic for PD is the presence of cytoplasmatic eosinophilic alpha-synuclein inclusions in the form of Lewy bodies in cell somata and Lewy neurites in axons and dendrites (Braak et al., 1999; Gibb and Lees, 1989). It has been suggested that alpha-synuclein could act like a prion protein during PD pathogenesis. In this theory pathologic, misfolded alpha-synuclein is an 'infectious' protein spreading pathology by forming a template that seeds misfolding for nearby alpha-synuclein protein, turning the previously healthy protein into a pathogenic protein (Jucker and Walker, 2013; Visanji et al., 2013).

Several clinical studies revealed that PD patients expressed alpha-synuclein accumulation in the ENS (Braak et al., 2006; Forsyth et al., 2011; Gelpi et al., 2014; Gold et al., 2013; Sánchez-Ferro et al., 2015; Shannon et al., 2012a). Alpha-synuclein accumulations are associated with damage in the enteric neurons and possibly underlie GI dysfunction (Gold et al., 2013; Sánchez-Ferro et al., 2015). They affect both the myenteric and submucosal plexuses of the gut in PD patients and are distributed in the GI tract from the esophagus to its most distal point, the rectum (Beach et al., 2010).

Braak and colleagues hypothesized that alpha-synuclein pathology might start in either the OB and/or in the ENS possibly by an unknown pathogen and/or environmental toxin and then progresses towards the SN and further areas in the CNS. The vagal nerve might provide a path for the spread of alpha-synuclein pathology from the ENS to the brain through the brainstem, midbrain, basal forebrain and finally the cortical areas (Braak et al., 2003; Hawkes et al., 2007), whereas the initiation of the pathological process in the OB can more directly affect the brain via the olfactory tract (Hawkes et al., 2009a, 2010; Klingelhoefer and Reichmann, 2015). Our recent studies (Forsyth et al., 2011; Keshavarzian et al., 2015) suggest that gut-initiated pathological processes in PD do not necessarily require a pathogen and/or an environmental toxin since they can be triggered by the intestinal microbiota.

3.2. Alpha-synuclein spreading from the enteric nervous system towards the brain

Environmental factors such as microorganisms, including nasal/gut microbiota, and toxins like pesticides might start a pathological process at two sites, in the OB and within enteric nerve cell plexus (Hawkes et al., 2009b), causing mucosal inflammation and oxidative stress and thereby initiating alpha-synuclein accumulation (Hawkes et al., 2010).

In accordance with this hypothesis it has been shown that alpha-synuclein can be retrogradely transported from the intestinal wall to the brain in rats (Holmqvist et al., 2014). Others have shown in vitro and in vivo that alpha-synuclein is transmitted via endocytosis to neighboring neurons (Angot et al., 2012; Desplats et al., 2009). In a transgenic mouse model for PD, alpha-synuclein was shown to be transmitted to engrafted neuronal precursor cells, where it created inclusions (Brundin et al., 2008; Desplats et al., 2009). Similarly, autopsies of PD patients who had received fetal mesencephalic transplants, showed alpha-synuclein accumulation in the grafted neurons (Kordower and Brundin, 2009; Li et al., 2008).

Moreover, in a recent study full truncal vagotomy was associated with a decreased risk of developing PD compared to highly selective vagotomy (affecting only acid producing portion of gastric body) or no vagotomy supporting the idea that the vagal nerve might provide a conduit to spread PD pathology from the gut to the brain (Svensson et al., 2015). Another study showed that PD-like neuropathology was mimicked by gastric administration of pesticide rotenone in mice and occurred in the absence of detectable levels of rotenone in the brain and blood (Pan-Montojo et al., 2010). The local effect of pesticides on the ENS might be sufficient to induce PD-like progression and to reproduce the neuroanatomical and neurochemical features of PD staging, from the ENS to the CNS. Two years later, the same research group showed that the progression of pathologically expressed alpha-synuclein towards the brain could be halted by the resection of sympathetic and parasympathetic nerves prior to oral rotenone treatment (Pan-Montojo et al., 2012). Since the mucosal sides in relation to OB and the ENS are exposed to substances from the environment through inhalation or ingestion, it seems plausible that environmental