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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

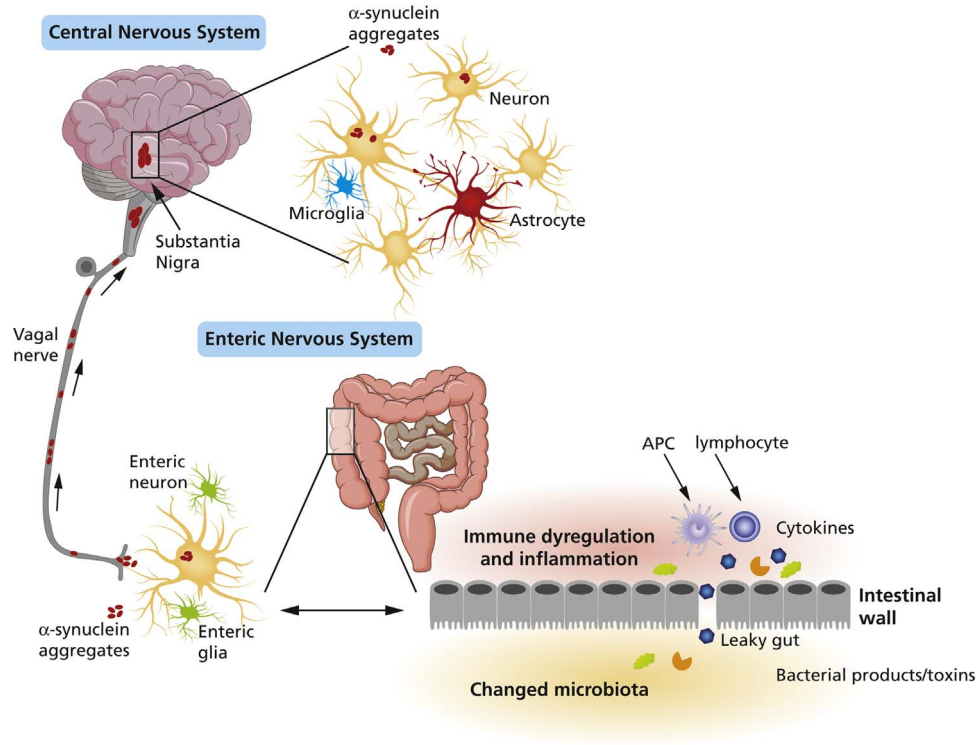

Fig. 1. A schematic representation of alpha-synuclein accumulation and spreading from the ENS towards the brain. Environmental factors such as microorganisms, including the gut microbiota, and toxins like pesticides might start a pathological process within enteric nerve cell plexus, causing mucosal inflammation and oxidative stress and thereby initiating alpha-synuclein accumulation. 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.

factors such as diets, toxins, intestinal microorganisms and other environmental pathogens might have an important role in triggering and propagating PD pathology, probably against a background of genetic vulnerability (Fig. 1).

3.3. Changes in gut bacterial composition

PD patients show an increased intestinal permeability, also known as leaky gut, that correlated with intestinal alpha-synuclein accumulation (Forsyth et al., 2011). The increased intestinal permeability and the translocation of bacteria and inflammatory bacterial products (e.g., lipopolysaccharide, LPS) might lead to inflammation and oxidative stress in the GI tract and thereby initiating alpha-synuclein accumulation in the ENS (Forsyth et al., 2011; Glass et al., 2010; Quigley and Quera, 2006). In addition, gut-derived LPS can promote the disruption of the blood brain barrier (Banks et al., 2008; Banks and Erickson, 2010) and thus facilitate neuroinflammation and injury in the SN that is triggered by the above stated environmental factors.

In support of this hypothesis, biopsies of colonic tissue retrieved from PD patients revealed an increased expression in the levels of pro-inflammatory cytokines, such as TNF-alpha, IFN-gamma, IL-6 and IL-1 beta as well as an increased activation of enteric glial cells (Devos et al., 2013).

There is now mounting evidence that the microbiota is altered in people suffering from PD. The first study demonstrating this was published in 2015 (Scheperjans et al., 2015) where a reduction of *Prevotellaceae* (77.6%) in fecal samples of PD patients was found. They further detected a relative abundance of *Enterobacteriaceae* that positively correlated with the severity of postural instability and gait difficulty (Scheperjans et al., 2015). The under-representation of *Prevotellaceae* diminishes the levels of health-promoting neuroactive short chain fatty acids (SCFA) and the capacity for biosynthesis of thiamine and folate (Arumugam et al., 2011), which is in line with decreased levels of these vitamins in PD patients (dos Santos et al., 2009; Luong and Nguyễn, 2013). The authors further indicate that a decrease in *Prevotella* might be related with a reduction in mucin synthesis which is associated with increased gut permeability (Brown et al., 2011; Forsyth et al., 2011) intensifying the translocation of bacterial antigens. In addition, a decreased abundance of *Prevotella* and an increased abundance of *Lactobacilliceae* have been associated with lower concentrations of ghrelin. Ghrelin is a gut hormone that may be involved in the maintenance and protection of normal nigrostriatal dopamine function (Andrews et al., 2009) and impaired ghrelin secretion has been reported in PD patients (Unger et al., 2011).

Another study from our group revealed differences in mucosal and fecal microbial community of PD patients in comparison to healthy subjects (Keshavarzian et al., 2015). The study showed a lower abundance of bacteria associated with anti-inflammatory properties such as of SCFA butyrate-producing bacteria from the genera *Blautia*, *Coprococcus*, and *Roseburia* in PD fecal samples, thereby concluding that a reduction in SCFA might contribute to gut leakiness. In addition, genes involved in lipopolysaccharide biosynthesis and type III bacterial secretion systems were higher in stool samples of PD patients compared to controls. Type III secretion systems are generally involved in pathogenicity and translocation of proteins that could facilitate bacterial product-induced inflammation (Galán and Collmer, 1999; Hueck, 1998). We concluded that PD pathogenesis may be caused or exacerbated by dysbiotic microbiota-induced inflammatory responses that could promote alpha-synuclein pathology in the intestine and the brain or by rostral to caudal cell-to-cell transfer of alpha-synuclein pathology caused by increased oxidative stress (due to an increase in pro-inflammatory bacteria).

A more recent study showed that not only gut microbiota but also fecal SCFA concentrations are reduced in PD patients compared to age-matched controls (Unger et al., 2016). They found a significant reduction of acetate, propionate and butyrate in PD fecal samples. The reduction in SCFA might induce alterations in the ENS and contribute to GI dysmotility in PD.

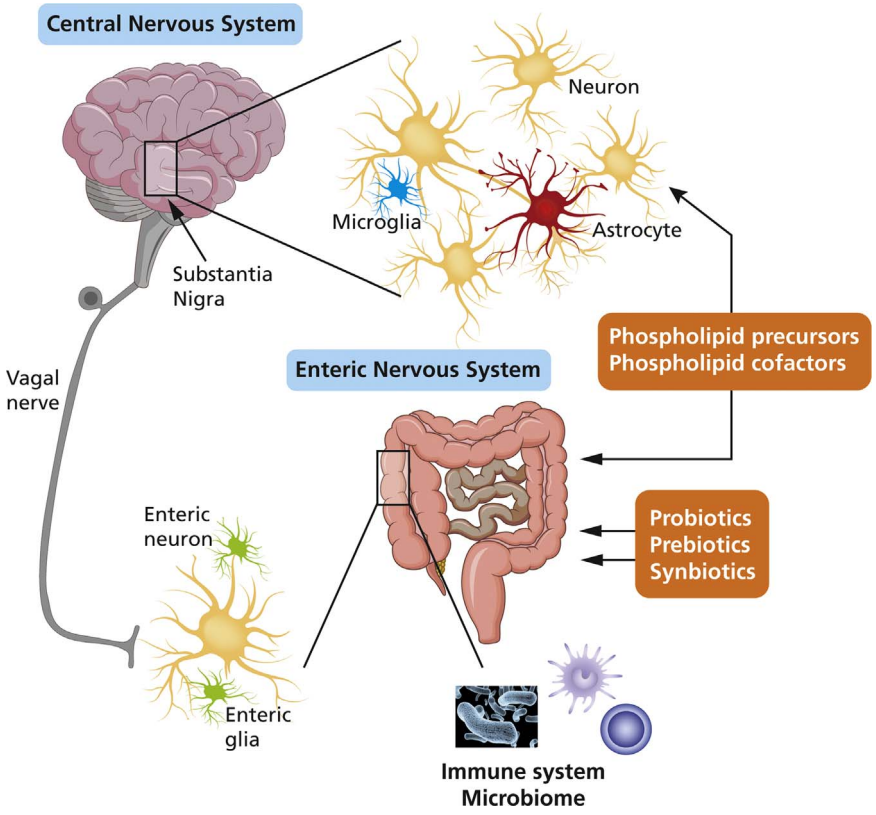

Fig. 2. Dietary phospholipid precursors and cofactors can increase neuronal membrane formation and function, and reduce inflammation, affecting both the ENS and CNS and reducing motor and non-motor abnormalities in PD. Probiotics, prebiotics and/or synbiotics might impact the gut microbiota composition, enhance intestinal epithelial integrity and reduce the pro-inflammatory response, impacting initiation or progression of the neurodegenerative process.

Moreover, SCFA butyrate has anti-inflammatory properties thought to be owing to an epigenetic mechanism or to the activation of SCFA receptors leading to anti-inflammatory effects, anti-microbial effects, and to a decreased intestinal barrier leakiness (Forsythe and Kunze, 2013; Ganapathy et al., 2013; Maslowski and Mackay, 2011; Singh et al., 2014).

Small intestinal bacterial overgrowth (SIBO) is a malabsorption syndrome associated with increased bacterial density and/or the presence of colonic-type species in the small intestine (Gasbarrini et al., 2007). Abnormalities of GI motility might increase the occurrence of SIBO which is highly prevalent in PD patients (Brown et al., 2011; Sánchez-Ferro et al., 2015), even in recently diagnosed PD patients (Tan et al., 2014). PD patients suffering from SIBO were not reported to develop worse GI dysfunction. However, they were independently predisposed to worse motor-dysfunction (Tan et al., 2014). SIBO might cause changes in intestinal permeability and contribute to an increase in bacterial translocation and therefore induce an inflammatory response (Chen and Quigley, 2014).

It is not possible to determine if changes in the gut microbiota are a cause or a consequence of PD pathogenesis. However, it might still play a role in neuronal loss by perpetuating inflammatory cascades and oxidative injury in the brain through LPS-mediated mechanism.

4. Current treatments for PD: interactions with GI dysfunction

Current anti-parkinsonian medication is based on compensating for dopaminergic cell loss and primarily targeted towards alleviation of motor symptoms by enhancing dopaminergic neurotransmission. The most commonly used symptomatic anti-parkinsonian agents are dopamine receptor agonists and the dopamine precursor L-3,4-dihydroxyphenylalanine (levodopa). The oral substitution of levodopa is, so far, the most regulative and efficient drug in the treatment of PD. Between 2001 and 2012, levodopa was used by 85% of patients suffering from PD, whereas dopamine agonists were used by 28% (Crispo et al., 2015). Unfortunately, levodopa treatment does not stop the disease progression and has major shortcomings. Many of the non-motor symptoms are unresponsive to dopaminergic treatments (Lee and Koh, 2015; Schrag and Quinn, 2000). The prolonged use of levodopa induces severe side effects such as dyskinesia and motor fluctuation (Schrag and Quinn, 2000) and as the disease progresses patients might eventually develop levodopa-resistance (Lebouvier et al., 2010; Lee and Koh, 2015). Moreover, it has been shown that levodopa-unresponsive features and constipation were positively associated with the amount of Lewy neurites in the ENS (Lebouvier et al., 2010).

Since levodopa treatment is taken orally, a good functioning of the GI tract is required in order to absorb the drug at a beneficial rate. Many efforts have been made to improve levodopa bioavailability by developing more effective oral formulations including combining levodopa with carbidopa to inhibit peripheral metabolism of levodopa. In addition, immediate and extended release levodopa-carbidopa oral formulations are under development (Freitas et al., 2016).

Several clinical studies revealed that single or multiple dosages of levodopa induced delayed gastric emptying in healthy volunteers (Epprecht et al., 2015; Robertson et al., 1992, 1990; Waller et al., 1991) and that it might therefore exacerbate the GI symptoms already developed in PD patients. Delayed gastric emptying in PD patients dampens the proper absorption of levodopa or dopamine agonists, causing lower peak plasma concentrations and on-off fluctuations of the drug (Doi et al., 2012; Hardoff et al., 2001; Marrinan et al., 2013). It would be interesting to test new therapies in combination with levodopa that could impact PD pathology and/or improve GI dysfunction and therefore improving levodopa uptake and availability. The dose of levodopa given to patients could then be lowered in the treatment of PD, reducing the negative secondary effects and possibly contributing to a longer beneficial use of the drug.

5. Targeting the gut-brain axis in Parkinson's disease with food-based therapies

No current therapeutic strategies have a favorable influence on PD progression. Moreover, none of them directly targets the gut-brain axis to prevent the spread of PD pathology or to alleviate non-motor as well as motor symptoms. Nutrition based interventions including phospholipid membrane precursors and/or microbiota-directed therapy like prebiotics and probiotics might provide opportunities to complement the traditional PD therapies and overcome some of their shortcoming including lack of efficacy for GI symptoms/dysfunction.

Dietary interventions might influence the gut-brain axis by altering microbiota composition (and therefore altering PD pathogenesis) (Clemente et al., 2012; Cryan and Dinan, 2012; Maslowski and Mackay, 2011) or by affecting neuronal functioning in both the ENS and the CNS (Fig. 2).

5.1. Nutritional membrane precursors and cofactors

Specific nutrient combination containing neuronal precursors and cofactors may counteract synaptic loss and reduce membrane-related pathology in the CNS and the ENS of PD patients. It might confer clinical benefits to patients suffering from PD since they are able to reduce motor and non-motor abnormalities in preclinical studies. Its combination with prebiotic fibers might have an added therapeutic value (Perez-Pardo et al., 2017a).

Synapse loss and membrane-related pathology provide compelling targets for interventions in PD. Uridine (as uridine monophosphate, UMP), the omega-3 fatty acid docosahexaenoic acid (DHA) and choline are phospholipid precursors needed for the formation and maintenance of neuronal membranes (Araki and Wurtman, 1998; Wurtman, 2014). They enhance the substrate-saturation of the enzymes responsible for the catalysis of the rate-limiting steps of phospholipids synthesis required for membrane formation (Van Wijk et al., 2014a, 2014b). Since phospholipids precursors are obtained basically from the circulation, increasing blood levels of these precursors with nutritional interventions might have a huge impact on the overall rate of phospholipid synthesis (Wurtman et al., 2009). In addition, cofactors in the synthesis of phospholipids, such as B-vitamins, vitamin C, vitamin E and selenium can increase the availability of the above mentioned membrane precursors by enhancing precursors uptake and metabolism (Van Wijk et al., 2014a, 2014b).

Several studies in rodents showed that co-administration of uridine, DHA, and choline can increase the amount of phospholipids, synaptic proteins, dendritic spine density and neurite outgrowth (Holguin et al., 2008; Sakamoto et al., 2007; Wurtman et al., 2006). The combination of these phospholipid precursors has also shown to partially restore dopaminergic neurotransmission in the 6-OHDA model of PD in rats (Cansev et al., 2008). A recent study demonstrated that dietary fat intake may modify the risk of developing PD directly or by altering the response to environmental neurotoxins; high levels of polyunsaturated fatty acids (PUFAs), like DHA decreased the association of PD with pesticides (Kamel et al., 2014). Individually, both uridine and DHA have been shown to induce favorable effects with preventive intake in animal models of PD (Bousquet et al., 2008; Delattre et al., 2010). In the 6-OHDA rat model, both DHA (Delattre et al., 2010) and uridine (Myers et al., 1995) reduced drug-induced rotational behavior. We have also shown the beneficial preventive effects of a dietary intervention containing uridine, DHA and choline in the unilateral rotenone model for PD. Intrastriatal injection of rotenone caused several motor and non-motor symptoms associated with PD. The preventive dietary intervention was not only effective for the mitochondrial dysfunction-induced motor symptoms but also reduced alpha-synuclein accumulation and inflammation in the colon (Perez-Pardo et al., 2017b). PUFAs, like DHA, have anti-inflammatory effects (Miller et al., 2009) and can improve mitochondrial dysfunction (Afshordel et al., 2014; Bazan et al., 2012) leading to a reduction in oxidative stress and alpha-synuclein accumulation. In another study we showed that the same diet given in a therapeutic setting (i.e. after the occurrence of full motor problems) in the intrastriatal rotenone model was also able to reduce motor dysfunction, colonic inflammation and alpha-synuclein accumulation in the ENS, demonstrating that the diet is not interacting with rotenone toxicity but rather has neurorestorative properties (Perez-Pardo et al., 2017a). The same study showed that an extended therapeutic nutritional intervention containing the same phospholipid precursors plus cofactors for phospholipid synthesis as well as prebiotic fibers (GOS and FOS) was more effective in normalizing motor and GI abnormalities. Adding cofactors to the diet might increase neuronal membrane formation by increasing the availability of membrane precursors or by directly affecting the neuronal membrane or membrane synthesis (Van Wijk et al., 2014a, 2014b) that might explain its better effects in motor-symptoms. In other in vivo studies, similar nutritional combinations have shown to be more effective than supplementation of single nutrients or incomplete formulations in animal models for Alzheimer's disease (Broersen et al., 2013; Janickova et al., 2015; Zerbi et al., 2014). Prebiotic fibers added to the diet might explain its better effects on GI-function since GOS and FOS have shown to have beneficial effects on immune function (de Kivit et al., 2011), bowel motility (Meksawan et al., 2014; Scholtens et al., 2014), but they might also contribute to its better efficacy on motor-function since the prebiotic fibers might positively affect microbiota composition that in turn can alter the enteric immune and nervous system and subsequently the CNS (Clemente et al., 2012; Cryan and Dinan, 2015; Maslowski and Mackay, 2011).

5.2. Probiotics

Probiotics are specific microorganisms that when administered in adequate amounts can exert a health benefit on the host by restoring microbiota and maintaining immune homeostasis (Reid et al., 2011). The most common probiotic bacteria currently used are representatives of *Lactobacilli*, *Enterococci, Bifidobacteria*, yeasts and mixtures of different beneficial bacteria (Varankovich et al., 2015). Various studies have reported the beneficial effects of probiotics by enhancing intestinal epithelial integrity, protecting from barrier disruption, stimulating a healthy homeostasis of the mucosal immune system and suppressing pathogenic bacterial growth (Ait-Belgnaoui et al., 2012; Corridoni et al., 2012; Patel et al., 2012; Sartor, 2005; Zareie et al., 2006). Moreover, different strains of probiotic bacteria have been shown to be effective in stimulating intestinal motility and reducing GI dysfunction. For example, in elderly orthopedic patients, probiotics showed to have positive effects on bowel movements by lowering the incidence of diarrhea and constipation severity (Zaharoni et al., 2011). In a double blind placebo controlled trial, *Lactobacillus reuteri* supplementation improved bowel movement frequency in adults with chronic functional constipations, but did not show to have an effect on stool consistency (Ojetti et al., 2014). Furthermore, studies have shown that is possible to modulate brain function by improving anxiety and depression using probiotics. In a mouse model of autism spectrum disorder (ASD), Hsiao and colleagues showed that the administration of *Bacteroides fragilis* reversed the abnormalities in gut permeability and ASD related behaviors (Hsiao et al., 2013). Ingestion of selected probiotics also exhibited beneficial effects on brain function in humans. The administration of *Lactobacillus casei* strain Shirota in chronic fatigue syndrome patients significantly decreased anxiety symptoms (Rao et al., 2009). Studies regarding the use of probiotics for the treatment of PD are very limited. One study showed that PD patients suffering from chronic constipation receiving fermented milk containing *Lactobacillus casei* Shirota for five weeks improved stool consistency and reduced bloating and abdominal pain (Cassani et al., 2011).

Probiotics might be a powerful tool in order to alter PD-associated microbiota composition and improve GI function and therefore reduce

gut leakiness, bacterial translocation and the associated neuro-inflammation in the ENS. Improving GI function by supplementation with probiotics might not solely lead to a better functionality and/or protection of the intestine, but might also improve levodopa absorption and reduce behavioral and cognitive deficits such as anxiety, depression and memory problems (Liang et al., 2015; Maes et al., 2008), which are common in PD patients.

5.3. Prebiotics

Prebiotics are non-digestible oligosaccharides, that beneficially affect the host by selectively stimulating the growth and/or activity of a limited number of bacteria in the gut (Gibson and Roberfroid, 1995). Two well-known non-digestible carbohydrates are the galacto-oligosaccharides (GOS), based on lactose and fructo-oligosaccharides (FOS), synthesized from fructose. GOS and FOS reach the colon more or less unchanged where they are metabolized by most of the *Bifidobacteria*, but only a few representatives of other strains. SCFA, lactose, hydrogen, methane, and carbon dioxide are metabolic products that lead to an acidic milieu in the colon, which antagonizes the survival and the proliferation of pathogenic bacteria (Kovács et al., 2014). SCFA are essential for the maintenance of intestinal epithelial integrity, and the homeostasis and regulation of mucosal immunological responses (Delzenne, 2003).

Prebiotic fibers have been shown to have beneficial effects on immune function (Jeurink et al., 2013)(de Kivit et al., 2011)(van Hoffen et al., 2009), bowel motility and constipation (Meksawan et al., 2014)(Scholtens et al., 2014)(Rasmussen et al., 2014) that might be very relevant for inflammation and GI-related symptoms in PD. Moreover, GOS and FOS have been shown to increase the levels of brain-derived neurotrophic factor (BDNF) in the dentate gyrus of the hippocampus in rats (Savignac et al., 2013). As BDNF signaling is critical for neuronal protection, survival and plasticity (Numakawa et al., 2010), GOS and FOS supplementation might have implications on brain neuroprotection.

Despite the evidence supporting the use of prebiotics for GI dysfunction, immune function, and neuroprotection, their use has never been investigated in patients with PD. Moreover, as mentioned above, the fecal microbial community of PD showed a lower abundance of SCFA butyrate-producing bacteria (Keshavarzian et al., 2015; Unger et al., 2016) that could be corrected by the use of prebiotic fibers.

5.4. Synbiotics

The term *synbiotic* is used when a product contains both probiotics and prebiotics. The term is reserved for products in which the prebiotic compound selectively favors the probiotic compound (Frei et al., 2015) (Schrezenmeir and de Vrese, 2001). Synbiotics have shown to have beneficial effects on immune function, dysbiosis and bowel function, very relevant for PD patients.

A clinical study showed that the probiotic *Lactobacillus salivarius* decreased inflammatory markers in healthy subjects, and its effect when *combined* with FOS was more pronounced (Rajkumar et al., 2015). Furthermore, another trial demonstrated that females with functional constipation and receiving *Bifidobacterium animalis* combined with FOS showed an increase in bowel movement, stool quantity and quality compared to controls (De Paula et al., 2008). As mentioned before, SIBO is highly prevalent in PD (Andrews et al., 2009; Brown et al., 2011) and PD patients that tested positive for SIBO are predisposed to worse motor-dysfunction (Tan et al., 2014). Interestingly, patients positively tested for SIBO treated with antibiotics followed by synbiotic supplementation, containing *Bacillus coagulans* and *FOS,* showed a better response than patients on the same regimen without synbiotic supplementation. 93% of the subjects treated with the synbiotic tested negative for SIBO compared to 67% of the controls. It also significantly decreased abdominal pain, flatulence and diarrhea (Khalighi et al., 2014).

6. Conclusion

To date, there is no treatment designed to cure PD. The most common used anti-parkinsonian medication is levodopa which does not prevent neurodegeneration, and has no effects on non-motor symptoms. Moreover, GI dysfunction in PD patients contributes to levodopa response fluctuations.

Current evidences indicate that alpha-synuclein deposition in PD might start in the ENS initiated by a toxin or pathogen and propagates to the CNS by transsynaptic cell-to-cell transmission. Bacterial translocation could also induce a pro-inflammatory environment that could signal to specific parts of the brain systemically and through dysfunctional blood brain barrier structures.

Therefore, a better understanding of the gut-brain interactions might bring new insight in PD pathological progression as well as lead to new therapeutic approaches. Pharmacological or dietary interventions should be aimed at alleviating both motor and non-motor symptoms.

Dietary membrane precursors and cofactors can increase neuronal membrane formation and function, and reduce inflammation, affecting both the ENS and CNS and reducing motor and non-motor abnormalities in PD.

Probiotics, prebiotics and/or synbiotics might impact the gut microbiota composition and possibly enhance intestinal epithelial integrity and reduce the pro-inflammatory response, impacting initiation or progression of the neurodegenerative process.

The above mentioned food-based therapies might therefore have an influence in PD pathological progression. Moreover, these therapies have shown to have beneficial effects on GI dysfunction and when combined with levodopa treatment they might increase levodopa uptake and availability, allowing a reduction in the doses of levodopa given to patients and reducing the negative secondary effects produced by the drug.

These compelling pre-clinical data have provided strong scientific rationale to conduct high quality randomized placebo controlled trial to assess the effectiveness of dietary supplementation (such as phospholipid membrane precursors, microbiota-directed therapy or a combination of them) in PD patients.

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