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Dysbiosis of gut microbiota and microbial metabolites in Parkinson's Disease

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ABSTRACT

Gut microbial dysbiosis and alteration of microbial metabolites in Parkinson's disease (PD) have been increasingly reported. Dysbiosis in the composition and abundance of gut microbiota can affect both the enteric nervous system and the central nervous system (CNS), indicating the existence of a microbiota-gut-brain axis and thereby causing CNS diseases. Disturbance of the microbiota-gut-brain axis has been linked to specific microbial products that are related to gut inflammation and neuroinflammation. Future directions should therefore focus on the exploration of specific gut microbes or microbial metabolites that contribute to the development of PD. Microbiota-targeted interventions, such as antibiotics, probiotics and fecal microbiota transplantation, have been shown to favorably affect host health. In this review, recent findings regarding alterations and the role of gut microbiota and microbial metabolites in PD are summarized, and potential molecular mechanisms and microbiota-targeted interventions in PD are discussed.

1. Introduction

PD is a multifocal and progressively neurodegenerative disease that is mainly due to the loss of dopaminergic neurons in the *substantia nigra* pars compacta, and characterized by motor symptoms and non-motor symptoms. Despite the cardinal motor symptoms, such as tremor, bradykinesia and rigidity (Kalia and Lang, 2015), there are also a number of non-motor symptoms that occur and affect the quality of life in PD patients over time (Martinez-Martin, 2011). Gastrointestinal (GI) dysfunctions are well-recognized in PD patients and known to be initial symptoms that occur prior to motor symptoms. A range of PD-associated GI dysfunctions has been clinically identified, including weight loss, gastroparesis, constipation and defecation dysfunction (Cloud and Greene, 2011; Kim and Sung, 2015; Sung et al., 2014). Moreover, early involvement of GI dysfunction is considered a possible presymptomatic stage of PD (Shannon et al., 2012b; Tereshchenko et al., 2015).

As a complex and multisystem disease, a series of mechanisms have been identified in PD. Protein (α-synuclein) aggregation, calcium homeostasis, endoplasmic reticulum stress, mitochondrial functional impairment probably account for most PD pathogenesis (Goswami et al., 2017). However, GI dysfunction is reported to be a significant contributor to the pathogenesis of PD, and the gut may even act as a route for the spread of pathology to the central nervous system (CNS). This notion is supported by pathophysiologic evidence: α-synuclein (α-Syn) inclusions appear early in the enteric nervous system (ENS), then reach the brain by the glossopharyngeal and vagal nerves (Braak et al., 2003; Shannon et al., 2012a). Further, injection of human α-Syn fibrils into the gut tissue of healthy rodents is sufficient to induce aggregated α-Syn pathology within the vagus nerve and brainstem (Holmqvist et al., 2014). The gut also contains millions of bacteria, and the evidence for the functional effects of microbiota on the bi-directional communications between gut and brain, in PD, is being increasingly supported.

Gut microbiota consists of a diverse community of bacterial species in the GI tract, existing symbiotically with the human host. The formation of gut microbiota is influenced by a number of factors, such as diet, antibiotic treatment, type of delivery and breast-feeding (Delzenne and Cani, 2011). A healthy and stable gut microbiota community plays a vital role in maintaining homeostatic balance of barrier integrity (Shi et al., 2017), function, metabolism (Nicholson et al., 2012; Velagapudi et al., 2010) and immunity (Olszak et al., 2012) of the gut, as well as regulating the gut-brain axis (Diaz Heijtz et al., 2011). Recently, studies have highlighted the influence of gut microbiota on the gut-brain axis, and its potential role in CNS-related conditions and neuropsychiatric disorders, such as multiple sclerosis (Jangi et al., 2016b), autism (Strati et al., 2017), depression (Foster and Neufeld, 2014) and schizophrenia (Caso et al., 2016). Knowing that gut microbiota and microbial metabolites can significantly interfere with host metabolism, cognition, behavior and immunity (Cryan and O'Mahony, 2011; Foster and McVey Neufeld, 2013; Marques et al., 2010), the role of gut microbiota and microbial metabolites in PD pathogenesis has received increasing attention, and some phenotypic correlations have been shown recently (Hill-Burns et al., 2017b; Unger et al., 2016a). For example, alterations in the number and composition of gut microbiota and microbial

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metabolites are found in PD patients. Gut microbial dysbiosis has been found to be associated with PD, as reflected by a significant reduction of *Prevotellaceae* from fecal samples of PD patients, as compared to healthy individuals. Additionally, a direct correlation exists between the abundance of *Enterobacteriaceae* and severity of postural instability & gait difficulty (Scheperjans et al., 2015b). Thus, understanding the early interaction between the gut microbiota and the occurrence of PD will open new avenues for intervention, particularly for early diagnosis and early therapy of PD. In this review, detailed descriptions of alterations of gut microbiota and microbial metabolites are summarized, and the potential molecular mechanisms of gut microbiota and microbial metabolite dysbiosis in PD pathogenesis are discussed. In addition, microbiota-targeted interventions with therapeutic potential for PD are also discussed.

2. The role of gut microbiota in CNS disorders

2.1. Gut microbiota help maintain microglia and the blood brain barrier (BBB)

There is already a growing acceptance that gut microbiota constantly controls the development and function of both the ENS and CNS (Hyland and Cryan, 2016; Sharon et al., 2016). Recent studies have provided numerous examples illustrating how gut microbiota modulates brain immune response and function. Studies on germ-free (GF) animals showed that depletion of a host's resident microbiota markedly compromised microglia cell shape and maturation, leading to blunted early responses following microbial-related molecule or pathogen challenge, such as exposure to lipopolysaccharide (LPS) and lymphocytic choriomeningitis virus. In contrast, recolonization with a complex microbiota can partially restore microglia features (Erny et al., 2015b). In addition, global defects of microglia, involving altered cell number and immature development, occur in the absence of a complex host microbiota, and can directly lead to impaired immune responses that then result in pathogenesis of CNS diseases, suggesting that gut microbiota and microbial metabolites are central to the maturation and function of microglial cells (Erny et al., 2015b). Permeability of the BBB has also been confirmed to be associated with gut microbiota and microbial metabolites. In the absence of gut microbiota, the BBB is more permeable to macromolecules compared to conventional (specific-pathogen-free) animals, and results from decreased expression of key tight-junction proteins in the brain endothelium. Furthermore, permeability decreases upon colonization of gut microbiota or upon administration of the short-chain fatty acids (SCFAs) butyrate, which is normally produced as a result of bacterial fermentation in the gut (Braniste et al., 2014).

2.2. Gut microbial dysbiosis in CNS diseases except PD

Recently, gut microbiota has been shown to play a fundamental role in deeply interconnecting gut and brain which widely accepted by microbiota-gut-brain axis (Bercik, 2011). In particular, in various CNS diseases, both clinical and experimental evidence has suggested the existence of dysbiosis of gut microbiota and microbial metabolites. For example, alterations in the composition of gut microbiota, involving increases of *Methanobrevibacter* and *Akkermansia* and decreases of *Butyricimonas at the genus level,* are observed in multiple sclerosis patients, and those microbial changes correlate with variations in the expression of genes involved in dendritic cell maturation, and interferon signaling and NF-κB signaling pathways in circulating T cells and monocytes (Jangi et al., 2016a). In Autism spectrum disorder (ASD) children, *Desulfovibrio* species and *Bacteroides vulgatus* are present in significantly higher quantities than in healthy individuals, and *Bacteroidetes* is found at high levels in severely autistic individuals (Finegold et al., 2010). Another study revealed that prominent dysbiosis in the gut microbiota of ASD children, with higher relative abundances of the microbial families *Lactobacillaceae*, *Bifidobacteriaceae*, and *Veillonellaceae,* and a particularly high abundance of genus *Lactobacillus* compared with healthy control children (Pulikkan et al., 2018). Recent studies also suggest that lower *Bifidobacterium* and/or *Lactobacillus* counts are more common in individuals with major depressive disorder, and conversely *Bifidobacterium* and *Lactobacillus* in the gut have been suggested to have a beneficial effect on stress response and depressive disorder (Aizawa et al., 2016). Moreover, *Enterobacteriaceae* and *Alistipes* have been found to increase, whereas *Faecalibacterium* is significantly reduced in individuals with major depressive disorder, compared to healthy controls, and a negative correlation has been observed between *Faecalibacterium* and the severity of depressive symptoms in patients with major depressive disorder (Jiang et al., 2015). In Alzheimer's disease (AD), the most common form of dementia, gut microbial diversity has been shown to be decreased in patients compared with control age- and sex-matched individuals, with decreased *Firmicutes*, increased *Bacteroidetes*, and decreased *Bifidobacterium* being specifically observed in the microbiota of AD patients (Vogt et al., 2017b). In particular, gram-negative intestinal bacteria of *Bacteroides*, increased in patients with AD, may result in increased translocation of LPS from the gut to the systemic circulation, which in turn may contribute to or exacerbate AD pathology through neuroinflammation. Moreover, certain species of *Bifidobacterium*, decreased in AD, are associated with anti-inflammatory properties and decreased intestinal permeability (Vogt et al., 2017a). One recent study on gut microbiota in multiple system atrophy (MSA) reported a five-fold reduction in *Paraprevotella* abundance at the operational taxonomic unit (OTU) level, and a five-fold reduction in *Paraprevotella* and four-fold increase in *Bacteroides* at the genus level in MSA patients compared with control individuals (Elahi, 2018). Interestingly, increased *Bacteroides* indicates disruption of mucous homeostasis and the intestinal barrier in MSA (Engen et al., 2017). All evidence about gut microbiol dysbiosis in CNS diseases except PD mentioned above are summarized in Table 1.

2.3. Dysbiosis of gut microbiota and microbial metabolites in PD

Much evidence has accumulated to show that PD is accompanied by dysbiosis of gut microbiota and alterations of microbial metabolites. In fact, a high prevalence of *Helicobacter pylori (H. Pylori)* infection among PD patients was reported many years ago (Charlett et al., 1999). Subsequent investigations have found a 50% prevalence of *H. pylori* seropositivity among Indian PD patients, suggesting that the presence of *H. pylori* infection may have been previously missed due to the symptoms of dyspepsia and gastric irritation occurring as a non-motor manifestation of PD, or by being considered a side effect of levodopa (Mridula et al., 2017). In addition, characterized by a malabsorption syndrome and increased bacterial density above 10^5 colony-forming units/mL of

Table 1
Altered gut microbiota composition in patients of CNS diseases.

Diseases	Altered microbiota	References
Multiple sclerosis	*Methanobrevibacter* ↑, *Akkermansia* ↑, *Butyricimonas* (butyrate producer) ↓	Jangi et al. (2016a,b)
Autism spectrum disorder	*Lactobacillaceae* ↑, *Bifidobacteriaceae* ↑, *Veillonellaceae* ↑ *Lactobacillus* ↑	Pulikkan et al. (2018)
	Desulfovibrio ↑, *Bacteroides vulgatus* ↑ , *Bacteroidetes* ↑	Finegold et al. (2010)
Major depressive disorder	*Bifidobacterium* ↓, *Lactobacillus* ↓	Aizawa et al. (2016)
	Enterobacteriaceae ↑, *Alistipes* ↑, *Faecalibacterium* ↓	Jiang et al. (2015)
Alzheimer's disease	*Bacteroidetes* ↑, *Bifidobacterium* ↑, *Firmicutes* ↓	Vogt et al. (2017a,b)
Multiple system atrophy	*Bacteroides* ↑, *Paraprevotella* ↓, *Paraprevotella* ↓	Elahi (2018)