Commentary

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The Role of the Gut in Parkinsons Disease

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Introduction

Parkinsons disease (PD) is the second most common neurodegenerative condition worldwide and is characterized by dopamine deficiency and Lewy body deposition composed of abnormal alpha-synuclein in the surviving neurons of the substantia nigra [1,2]. While the motor features of PD are well documented its pre-motor features are increasingly becoming recognized with constipation the most frequently reported. This is often associated with small gut intestinal bacterial overgrowth and *Helicobacter pylori* which are known to worsen motor symptoms [3]. It is because of this the possible role of the gut in PD pathogenesis is being investigated as described by Braaks Hypothesis [4]. Within the gut lies the microbiome, home to an estimated 100-trillion bacteria, two-thirds of which are unique to each individual and are inherited maternally at birth [2,3]. While 50% to 60% of these bacterial species are yet to be cultured it was thought that their function was to aid digestion and vitamin synthesis however in recent years the existence of a bidirectional gut-brain axis mediated by the vagus nerve which incorporates autonomic/enteric nervous systems and overlapping endocrine/immune systems has been recognized [2,3]. This relationship is evident by the identification of cholinergic anti-inflammatory pathways in the CNS to the gut and the role of gut bacteria in microglia maturation [5,6]. The enteric nervous system consists contains a significant proportion of dopaminergic neurons [6]. In addition, half of the body's dopamine production is made by gut bacteria with gut Lewy-body burden correlating with vagal nerve distribution [3,7].

A recent epidemiological study has found that patients with full versus highly-selective truncal vagotomy were less likely to develop PD. The dissemination of alpha-synuclein from the gut to the brain is therefore thought to occur through retrograde and anterograde axonal transport of alpha-synuclein alongside evidence of prion-like transmission in neurons [1]. It is because of this that the utility of alpha-synuclein in the gut as an early biomarker of PD has been questioned. Indeed a recent systematic review exploring this concept showed that it had a sensitivity of 81.1% to 82.2% but a poor specificity which may hamper correct diagnosis. It did, however, confirm that the finding of gut alpha-synuclein is specific to this group of patients but would need to be used in conjunction with other novel biomarkers to aid diagnosis before motor manifestations [8]. PD patients have been shown to have increased intestinal permeability that correlates with the alpha-synuclein burden. Evidenced by the high levels of mucosal staining for *E. coli* and high serum levels of lipopolysaccharide found within animal models of PD culminating in a pro-inflammatory state which can alter blood-brain-barrier integrity [1,9]. It is therefore hypothesized that through increased gut permeability, bacteria and neuroactive molecules translocate leading to local inflammation and misfolding of host alpha-synuclein which when recognized by Toll-Like-Receptor 2 primes the immune system leading to inflammation which is enhanced by CNS microglia **(Figure 1)**. This is evidenced by the finding that Lewy bodies can activate via TLR 2 and TLR4 receptors inflammation within the surrounding area of alpha-synuclein deposition. Recent evidence has highlighted in both animal and human modes that oxidized alpha-synuclein within the gut and substantia nigra is a major T-cell antigen and upon activation leads to immune cell infiltration (particularly Th17 and Th1 subsets) of the substantia nigra and microglial activation leading to a cascade of immune cell activation originating from the dysbiosis of the gut [10].

This is fascinating as germ-free animals who overexpress alpha-synuclein do not exhibit PD symptoms [5-7,9]. This change in permeability, however, may be secondary to microbiota alterations. Consistently, lower levels of *Preveotella* have been found in PD patients than in age-matched controls. Prevotella is important in short-chain fatty acid synthesis which has anti-inflammatory properties, are key constituents of the intestinal barrier and modulate microglia maturation [9]. Other changes include increases in *A. Mucinphila* which is known to degrade mucin, decreased clostridium populations linked to Regulatory T-cell function and mucosal integrity and increased levels of cyanobacteria which are known to produce B-N-Methyl- amino alanine an excitotoxin linked to host protein misfolding and neurodegenerative disease [2,11].

The role of bacteria in PD pathogenesis is highlighted by the fact that gut bacteria from PD patients can produce motor features in genetically susceptible mice [6]. However, do these changes predate PD symptomology? Rotenone allows one to study PD in animals. After 4-weeks exposure mice exhibit constipation, increased intestinal deposition of alpha-synuclein and an increased fecal *Firmicutes: Bacteroidete* ratio before demonstrating motor symptoms. These two bacterial species represent the most abundant gut organisms and their imbalance has been linked to several pathologies and are the target of

potential therapies such as minocycline which exhibits some neuroprotective effects in PD [2,5,11].

At present the mainstay of PD treatment is Levodopa. This aims to replace the deficiency of dopamine within CNS and minimize symptoms. Currently, it is the single best treatment however it is known the bioavailability of levodopa differs significantly amongst PD patients with its effectiveness waning with time with increasing 'off' time periods reported by patients. Levodopa has recently been shown to be metabolized in the jejunum to dopamine by *Enterococcus* and *Lactobacillus* which express the enzyme tyrosine decarboxylase it is thought that this explains the increased levodopa doses required to ameliorate symptoms in late disease. This highlights the need to understand gut biology in order to maximize the effects of therapy in the management of PD [12].

Dietary changes, therefore, affecting such populations, however, may be key in affecting microbiota populations and PD progression. Diets rich in neuronal components (e.g. uridine) have been found to partially restore dopaminergic neurotransmission while dietary polyunsaturated fatty acids (omega 3-DHA) can reduce motor symptoms and inhibit Toll-Like- Receptor 2 activation. However, what if we were to influence the gut bacteria themselves? Probiotics are specific microorganisms which can exert a health benefit by restoring microbiota with *lactobacillus* helping resolve constipation in PD [1,5]. Prebiotics, non-digestible oligosaccharides act to facilitate the outgrowth of a single/multiple bacterial species. Two preparations Galactooligosaccharide and Fructooligosaccharide have been shown to increase the levels of Brain-Derived Neurotrophic Factor which alters neural plasticity and can help normalize motor features in animal models of PD [9,13].

Discussion

As such possible bacterial population manipulation in human trials is the next stage of PD research and is something that is already being investigated. Indeed, unlike other accepted Parkinson Disease treatments such as Deep Brain Stimulation (DBS), this is a relatively safe option which may exhibit synergism with existing treatments. Finally, it seems we may have a promising direction in which to try and curtail the Parkinson disease burden.

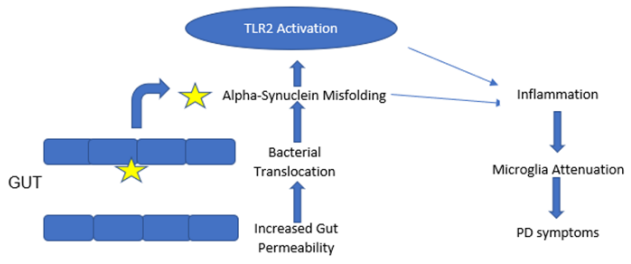

Figure 1: Possible pathogenesis of Parkinsons Disease (PD) as a result of altered gut permeability.

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