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Review Article

A Review on Cognitive Impairments in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is one of the most significant medical and social burdens of our time. It is a multifactorial neurodegenerative disorder, affecting 3.7% of the population over 65 years of age. PD involves degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNPC) with deficiency of dopamine. Anxiety is frequent in Parkinson's disease (PD) and has a negative impact on disease symptoms and quality of life. The underlying mechanisms remain largely unknown. Several evidences provide support for involvement of the microbiota-gut-brain axis in PD pathogenesis. In this review, we intend to provide a comprehensive overview of current knowledge on how cognitive behavior deficit occur in PD, and its potential as a new target of therapeutic interventions for PD.

Keywords: Anxiety; Dopamine; Gastrointestinal; Microbiota; Pars Compacta; Pathophysiology

Introduction

Parkinson's disease (PD) is a movement disorder, which includes motor as well as non-motor symptoms. It can be recognized through its motor impairments including, bradykinesia (slowness of movement), rest tremors, muscle rigidity, postural instability and gait disturbances [18]. Non-motor symptoms of PD include cognitive deficits (mild cognitive impairment to PD-related dementia), autonomic dysfunction, disorders of sleep, depression and hyposmia. A range of gastrointestinal (GI) symptoms involving gastrointestinal tract (GIT) motility [19], constipation, dry mouth and gastroparesis are the prevalent risk factors for PD [10].

Important clinical aspect of motor and non-motor symptoms

In addition to bradykinesia, which is a core symptom, different types of tremors occur. Whereas the rest tremor is characteristic, action tremor, re-emergent tremor and orthostatic tremor may occur in Parkinson's disease. In spite of effective symptomatic therapy, the underlying disease continues to progress with the emergence of motor fluctuations, dyskinesia and freezing of gait (FOG). Non-motor manifestations such as cognitive dysfunction and autonomic problems tend to become disabling in advanced Parkinson disease. The term Parkinson syndrome may be preferable, as the disorder may not be a single clinico-pathological entity.

Cognitive impairments

In late-onset of PD, Cognitive impairment represents the main non-motor burden of disease. It is associated with increased mortality rate, poor functional prognosis, institutionalization and health related quality of life deterioration [33,42]. Due to variable time to progression to dementia, the onset of cognitive impairment cannot be predicted by duration of illness and age alone. Hence, it is necessary to find out biomarkers of cognitive impairments in PD, which may include utility of eye tracking, as impairment in eye movement is most frequently found in PD's patients. The control of eye movement involves complex neural circuitries overlapping with cognitive controls; therefore, pathologies could affect

these functions concurrently. At the same time in patients of PD, it is well-established that cognitive impairment is highly heterogeneous in terms of cognitive domains affected and pathophysiological underpinnings [13]. According to [13], not only a single biomarker will share pathophysiologies of distinct degenerative mechanisms to predict or reflect the whole spectrum of cognitive impairment.

The pathogenesis of Post Operative Cognitive Dysfunction (POCD) is not yet elucidated. However, current studies have suggested the major pathogenesis of POCD is CNS inflammation. The immune system of the body could be activated by surgical trauma which induces the release of peripheral cytokines. The normal function of Blood-Brain Barrier (BBB) is to restrict the immune cells and various inflammatory factors from entering the brain but the abnormal structure of BBB exposes the CNS in harmful substances in circulation and transduction of immune signals to brain take place which induce the CNS inflammation, leads to nervous system dysfunction and cognitive impairments. An experiment of dynamic contrast-enhanced magnetic resonance imaging was done to investigate the moderate cognitive impairment in aged patients and it was found that BBB breakdown in hippocampus could be an early independent factor responsible for the inducement of cognitive impairment in aged patients [29].

In the elderly, the major pathophysiological mechanism of POCD is increased BBB permeability [45]. Mix effect of antibiotic and aging decreased the expression of Tight Junction (TJ), which leads to increased BBB permeability and induced POCD; this all could be reversed by the application of Sodium Butyrate (NaB) and *Lactobacillus*. NaB and *Lactobacillus* increased the expression of TJ protein between Endothelial Cells (ECs), which reduced the permeability of BBB and hence protected the POC functions of the gut dysbiosis and aged mice. Gut microbiome also improves postoperative cognitive function by decreasing BBB permeability in aged mice [40].

NaB, a vital component of short chain fatty acids (SCFA), upregulates the expression of TJ between ECs and, hence, increased the integrity of BBB which ultimately leads to the protection of nerves [26,32]. Cognitive behavioral therapy has also demonstrated benefit by adjustment of automatic thoughts and harmful behavior patterns, also by identification and guiding insight into internal emotions and psychoeducation of pain and fatigue when they are present [12,25,39].

[14,22] assessed the integrity of BBB in PD and they showed no change in its function in MPTP induced mouse model as well as permeability studies of levodopa designed for PD treatment, which suggests that BBB remains intact in PD. Whereas other researchers proved that intestinal permeability is influenced by gut microbiota also observed from PD patients as well as animal models of PD that they possess compromised intestinal permeability, hence, suggested a point of convergence between intestinal permeability and neuroimmune responses [6,34,38]. [20] performed PET imaging study among PD patients and they observed deficiencies in cerebral blood flow that had a close correlation with motor dysfunction and levodopa treatment, [48] accounted VEGF-driven increased BBB permeability and angiogenesis. [43] found FITC-labeled albumin leakage filled with activated microglia, indicating that microglia may directly affect BBB dysfunction in PD. These activated microglia induce the release of pro-inflammatory cytokines, which induce protein rearrangement and alter protein expression in TJ [26]. [5] demonstrated by findings that increased levels of IL-6, IL-1β and TNF-α in the brain decreased the tight junction proteins *i.e.* occluding and ZO-1 which correlates with a reduction in trans-endothelial electrical resistance. Thus it can be concluded that leaky BBB, microglia and astrocytes are key players in PD.

[15] concluded that lipopolysaccharide (LPS) from gut microbiota can alter BBB functions directly or indirectly via regulating TJ expression and BBB integrity, they also explain another potential mechanism that gut bacteria influence BBB permeability is the metabolite (SCFAs, BA, propionic acid) that can alter CNS function. Bacteria producing high levels of butyric acid like *Clostridium tyrobutyricum* improves BBB integrity in Germ-Free mice, is associated with an up-regulation of TJ protein expression. This bacteria strain, however, is decreased in PD patients [15]. The propionate receptor FFAR3 is expressed on human brain endothelium highlighting the role of propionate in BBB integrity. *In vitro*, propionate exerted protective effects on BBB integrity by suppressing non-specific microbial infections through a CD14-dependent mechanism, expression of LRP-1 and oxidative stress [3]. In addition, lipoteichoic acid (LTA), produced by bacteriolysis, is found to induce the secretion of cytokines IL-1β and TNF-α [35] and is required for anchoring microorganisms to brain microvascular endothelial cells that disrupt

the BBB [28]. It is also discovered by researchers that purified LTA can selectively stimulate TLR2, which causes peripheral immune activation, and neuroinflammatory processes in the brain. These immunologic changes took place in parallel with a transcriptional up-regulation of cytokine and down-regulation of tight junction-associated proteins [23]. [40] showed that antibiotic and aging increase blood vessel permeability of hippocampus BBB and also lead to damage in TJ structure between ECs in mice along with decreased spatial memory learning ability. However the application of *Lactobacillus* mix or NaB significantly reverses these adverse effects of gut dysbiosis and aging in mice [37,40]. Hence it is demonstrated that Lacto and NaB can improve TJ between the ECs, ultimately the BBB permeability in gut dysbiosis and aged mice, thereby preventing POCD in such animals [24,26,32,40].

How the biological products from gut reach the CNS is an important question. In patients with PD, [9] have detected microstructural abnormalities in brain capillaries. They also observed increased density of ECs in vasculature with substantia Nigra, but not in surrounding neurons (i.e. ventral tegmental area) [11]. These abnormalities have been attributed to damage induced by reactive oxygen species (ROS) released by activated microglia [4]. LPS inducement in animal models leads to disruption in BBB with relative selectivity for the thalami, cerebellum, frontal lobe and brainstem [1] whereas [17] showed that BBB seems more vulnerable to LPS in mice that expresses alpha-synuclein as compared with knock-out mice for alpha-synclein. Hence it can be concluded that alpha-syn has a role in BBB integrity. [4] performed experiment and provided evidence for increased angiogenesis primarily involving the putamen and the pars compacta of SN in patients with PD. Newly formed vessels within the CNS make the BBB vulnerable to leakage of neurotoxic molecules or inflammatory cells [16]. An increased expression of Vascular Endothelial Growth factor (VEGF) has been correlated with the number of blood vessels in close proximity with the degenerating dopaminergic neurons in MPTP induce monkeys compared to control monkeys [2]; but [46] observed increased expression of VEGF in the striatum of PD patients; this finding occurs without a compensatory increase of the "Pigment Epithelium-Derived Factor" (PEDF), an anti-angiogenic molecule with reciprocal regulation with VEGF and protective effects to some neurons [46,47]. [16] reported increased angiogenesis biomarkers such as the VEGF; one of its receptors (VEGFR-2) and the Placental Growth Factor (PlGF) in the CSF of patients with PD. Some researcher has linked dyskinesia with angiogenesis [31,41]. [31] observed pharmacological inhibition of VEGF attenuated BBB hyper-permeability and dyskinesia in an experimental animal model and the same group in PD patients with history of dyskinesia, postmortem tissue has shown increased microvascular density along with upregulation of VEGF mRNA. In summary, it can be concluded that increased micro-angiogenesis and BBB hyper-permeability seems to increase after the exposure of basal ganglia's neurons and glia to systemic and gut derived neurotoxins and inflammatory cells, contributing to degeneration of neurons [20].

ZO-1 and occludin are two important TJ associated proteins conferring physical barrier function in both the brain and intestine. [8] performed an experiment on mRNA expression of ZO-1 and occludin in SNpc of brain and colon. They observed that MPTP injection resulted into decreased occluding mRNA expression in both colon and SNpc but MPTP has shown no effect on ZO-1 mRNA expression. They also found that polymannuronic acid improved integrity of both the intestinal barrier and BBB in PD mice.

SCFAs have the ability to cross and influence BBB via inhibiting pathways associated with inflammatory responses in brain, hence it could act as neuromodulators, provide neuroprotection by inhibiting neuroinflammation [23,27]. SCFAs also modulate synthesis of neurotransmitter (5-HT) along with the expression of their receptors [30]. [44] concluded that damage to BBB resulted into death of dopaminergic neurons while protection of BBB slows down degeneration of neurons and progression of PD.

Consistently, Polymanuronic acid (PM) could induce colon Casp14 and Tff2 gene shown in our RNA-sequencing results, these genes were reported to benefit epithelial integrity and intestinal mucosa integrity [21,36]. Hence, it is concluded that PM possesses neuroprotective effects via showing anti-inflammatory actions in the brain, gut, and systematic circulation. Improvement of integrity of intestinal barrier and BBB in response to PM intake was observed [8]. It occurred may be due to increased SCFAs and [7] also found that in neurological disorders, SCFAs from colonic dietary fiber or polysaccharides fermentation are important mediators for their roles in anti-inflammatory processes, promotion of BBB and neuro-modulation.

Conclusion

Nowadays the CNS diseases, in particular the neurodegenerative disorders e.g. Parkinson's disease, constitute a serious health prob-

lem that increasingly affects global population, involving a great morbidity and mortality. The current review indicates that PD is associated with dysregulated immune responses, dysfunctioning in BBB and changes in gut microbial composition. It involves lowered abundance of a range of specific SCFA, particularly butyrate producing bacteria. However, the mechanisms of PD pathophysiology are unlikely to be solely a lack of SCFAs. Rather, a combination of factors including increased pro-inflammatory bacteria, greater intestinal permeability, introduction of a neurotropic pathogen and small intestinal bowel overgrowth, are likely additionally responsible. Despite this, additional research is needed to address how these gut microbiota differences and BBB dysfunctioning is related to PD duration and symptoms, and if these divergences are still present when accounting for confounding lifestyle and health factors.

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Conflict of Interest

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