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ORIGINAL

THE INFLUENCE OF HOMOCYSTEINE AND THE GUT-BRAIN AXIS ON MOTOR FUNCTION AND NEUROMUSCULAR ADAPTATION IN PARKINSON'S DISEASE: IMPLICATIONS FOR PHYSICAL ACTIVITY AND REHABILITATION

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ABSTRACT

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons and the accumulation of α-synuclein (α-syn) in the substantia nigra, leading to both motor and non-motor dysfunctions. While PD primarily manifests as a movement disorder, increasing evidence suggests that gastrointestinal (GIT) dysfunction and systemic metabolic disturbances play a crucial role in its progression. Elevated homocysteine (Hcy) levels, often observed in PD patients due to genetic factors, L-dopa therapy, malnutrition, age, and sex, have been linked to accelerated neurodegeneration, vascular inflammation, and impaired neuromuscular function, potentially exacerbating disease symptoms and affecting physical performance and rehabilitation outcomes. **Objective**: This review examines the role of hyperhomocysteinemia (HHcy) in gut-brain axis dysfunction, its impact on intestinal microbiota, inflammatory responses, and α-synuclein aggregation, and its potential consequences for neuromuscular adaptation, motor control, and physical rehabilitation in PD patients. **Methods**: A comprehensive analysis of existing literature was conducted to explore the association between HHcy, intestinal dysbiosis, microvascular dysfunction, and neuroinflammation in PD. Special emphasis was placed on how Hcy-related metabolic disturbances influence physical function, gait stability, and rehabilitation potential in PD patients. **Results**:

Findings suggest that elevated Hcy levels contribute to intestinal flora dysregulation, increased inflammation, and microvascular impairment, which may further exacerbate dopaminergic neurodegeneration and neuromuscular dysfunction. Additionally, HHcy-induced systemic inflammation and gut microbiome disturbances appear to aggravate neuroinflammation through the gut-brain axis, potentially worsening motor impairments and reducing adaptability to physical therapy and exercise interventions. Given that exercise and targeted rehabilitation programs are crucial in maintaining mobility, muscle coordination, and neuromuscular function in PD, understanding the metabolic role of Hcy can inform novel therapeutic strategies to enhance physical resilience and motor performance in PD patients. **Conclusions**: HHcy is a critical metabolic factor that influences both neurodegeneration and motor function deterioration in PD, with significant implications for rehabilitation, exercise capacity, and neuromuscular adaptation. Future research should focus on developing targeted interventions, including dietary strategies, pharmacological treatments, and structured exercise programs, to mitigate the effects of HHcy on both the gut-brain axis and motor function. Integrating nutritional and physical activity-based interventions may provide a more comprehensive approach to PD management, improving functional outcomes, mobility, and overall quality of life in affected individuals.

KEYWORDS: Parkinson's Disease, Homocysteine, Gut-Brain Axis, Enteric Microbiota, Gastrointestinal Dysfunctions, α-synuclein

1. INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons in the substantia nigra and the accumulation of α-synuclein aggregates, leading to motor impairments such as tremors, bradykinesia, rigidity, and postural instability. While PD is often classified as a movement disorder, non-motor symptoms—including gastrointestinal (GIT) dysfunction, systemic inflammation, and metabolic disturbances—frequently precede the onset of motor symptoms, indicating a complex pathophysiological network involving the gut-brain axis. Recent evidence suggests that hyperhomocysteinemia (HHcy), a condition characterized by elevated levels of homocysteine (Hcy), may serve as a key metabolic factor influencing both neurological degeneration and physical function decline in PD patients.

1.1 The Role of Homocysteine in PD Progression and Neuromuscular Function

Homocysteine is a sulfur-containing amino acid that plays a crucial role in methylation and redox balance. Elevated Hcy levels in PD patients have been linked to L-dopa metabolism, genetic mutations, malnutrition, and age-related

metabolic inefficiencies. Studies indicate that HHcy may exacerbate neurodegeneration by promoting oxidative stress, microvascular dysfunction, neuroinflammation, and impaired mitochondrial function, all of which contribute to motor deterioration, muscle atrophy, and reduced adaptability to physical therapy interventions. Additionally, high Hcy levels are associated with endothelial dysfunction, which may affect cerebral blood flow and neurovascular coupling, further aggravating movement disorders in PD(Feigin et al., 2019). (Ascherio & Schwarzschild, 2016) (Parkinson, 2002) .

1.2 The Gut-Brain Axis and Its Influence on Motor Function and Physical Adaptation in PD

Emerging research highlights the gut-brain axis as a critical mediator of neurodegenerative processes in PD, with growing evidence that gastrointestinal dysfunction and gut microbiota dysbiosis play a role in α-synuclein aggregation and systemic inflammation. Non-motor symptoms such as constipation, intestinal permeability, and chronic gut inflammation are commonly observed in PD patients, often manifesting years before the onset of motor deficits. Hcy is partially produced in the intestines, and its accumulation is known to worsen GIT dysfunction, disrupt the intestinal microvasculature, and trigger neuroinflammatory pathways that accelerate PD progression. The interplay between HHcy, intestinal dysbiosis, and inflammatory signaling may have profound implications for neuromuscular adaptation, balance control, and the efficacy of rehabilitation strategies in PD patients(Sanderson et al., 2019).

1.3 Relevance to Physical Activity and Rehabilitation Medicine

Given the significant impact of PD on motor function, muscle coordination, and gait stability, structured exercise interventions and neuromuscular rehabilitation programs are essential components of disease management (Silla et al., 2019). However, metabolic imbalances such as HHcy may limit exercise capacity, contribute to muscle fatigue, and hinder postural control, increasing the risk of falls and movement-related complications. Understanding the metabolic role of Hcy and its effects on the gut-brain axis can provide valuable insights into developing personalized rehabilitation strategies that optimize neuromuscular performance, improve mobility, and delay functional decline in PD patients(Xiao et al., 2015). Recent epidemiological and experimental investigations have demonstrated a correlation between elevated levels of Hcy and many neurodegenerative disorders, such as stroke, Alzheimer's disease, and PD (Mattson & Shea, 2003). An empirical study utilizing a randomized controlled trial has demonstrated a positive correlation between elevated plasma total Hcy levels and a more pronounced decrease in PD patients' MMSE score (Christine et al., 2018). In addition, Karel Kalecky has documented that patients with PD and dementia exhibit an abnormal one-carbon metabolism, leading to the accumulation of Hcy

in the brain (Kalecký et al., 2022). Hcy has been observed to significantly impact the neurological system by raising inflammation and oxidative stress and reducing DNA methylation. There is ongoing debate on the connection between the pathogenic role of HHcy and the advancement of PD, which has yet to be fully understood(Table1).

Table 1: Graph of association between homocysteine and Parkinson's disease.

X	STUDY DESIGN NUMBER OF PATIENTS	DISEASE	RESULT REFERENCE
CHRISTINE ET AL.	Randomized Controlled Trial N=456	The early, untreated PD patients	Elevated homocysteine at baseline was (11) linked with worse scores on the baseline MMSE and greater annualized decline in MMSE
KALECKY ET AL.	Controled study N=65	Various stages of cognitive impairment PD patients	Non-demented PD subjects are able to (12) efficiently metabolize levodopa-induced Hcy, whereas PD patients with dementia have an impaired metabolism to cause elevation of Hcy
O'SUILLEABHAIN ET AL.	Prospective study N=90	PD patients with di ifferent treatment	Levodopa elevates Hcy level in PD (38) patients
BIALECKA ET AL.	Controled study N=248	PD patients into groups with dementia and without dementia	Hcy was increased in PD patients as (48) compared with the controls and was linked with the MTHFR 677C>T polymorphism.
RELIGA ET AL.	Controled study N=114	PD patients into groups with treated and non-treated	Hcy levels were associated with the (50) duration of PD and levodopa treatment
XIE ETAL.	A meta-analysis N=1560	PD patients	PD patients with cognitive dysfunction (109) were likely to have higher Hcy levels
ZHONG ET AL.	A Cross-Sectional study N=99	PD patients into groups with minor hallucinations and withou minor hallucination	High Hcy concentration was correlated (110) with PD patients with minor hallucination and also associated with PD patients with GIT dysfunction

1.4 Parkinson's disease pathogenesis: A closer look at the gastrointestinal system

PD has four typical manifestations: resting tremor, bradykinesia, rigidity, and postural deformities. However, during the initial PD stage, non-motor symptoms are also considered essential warning signs for clinical diagnosis (Jankovic & Tan, 2020) and include anxiety, pain, impulse control dysfunction, cognitive impairment, olfactory dysfunction, dementia, depression, psychosis, insomnia, rapid-eye-movement sleep behavior disorder (RBD), fatigue, and autonomic dysfunction [such as urinary incontinence, drooling, orthostatic hypotension, gastrointestinal tract (GIT) dysfunction, erectile dysfunction, excessive sweating]. Where GIT dysfunction is an important non-motor symptom (14, 15) because approximately 80% of PD patients indicate constipation, which is often preceded by the onset of motor symptoms (16). Constipation is considered a clinical index for diagnosing prodromal PD (17).

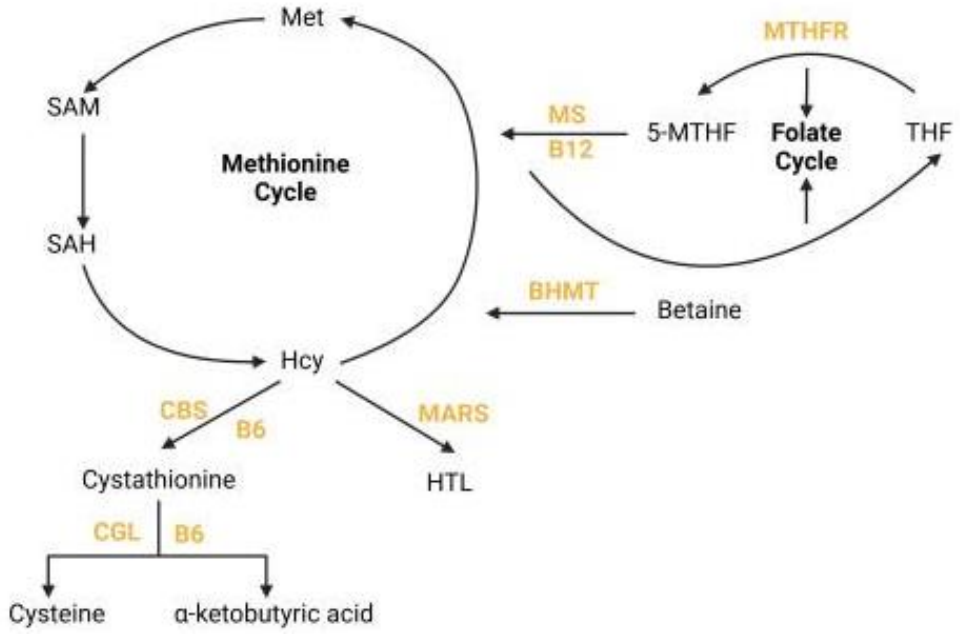
Evidence suggests that α-syn transgenic mice show aggregation of α-syn in the enteric nervous system (ENS) before any pathological changes are noticed in the central nervous system (CNS). This indicates that α-syn may be transmitted in a bottom-up manner (Salim et al., 2023). Consistently, previous Swedish and Danish studies have revealed that truncal vagotomy reduces PD development risk by 15 - 22%, confirming the involvement of the vagus nerve in the pathological transmission of α-syn in PD (Liu et al., 2017). Colonic tissue analysis and increased inflammatory markers in PD patient's feces have indicated that intestinal inflammation is another GIT characteristic of PD (Rolli-Derkinderen et al., 2020). Furthermore, the expression of tight junctional proteins, including zonula occludens-1(ZO-1) and claudin-5, is also reduced in colonic epithelial cells of PD patients (Clairembault et al., 2015). Moreover, leaky gut syndrome could be because of the complicated overlapping of α-synucleinopathy, enteric inflammation, and altered gut microbiota, which increases intestinal permeability and reduces tight junction proteins. Additionally, PD patients and animal models have indicated a relationship between gut dysbiosis, colonic α-syn accumulation, and fecal inflammatory markers (Rolli-Derkinderen et al., 2020).

Therefore, the "gut-brain axis" has become a hotspot for investigating the pathogenesis of PD. According to epidemiological research, in Western and Asian populations, the risk of PD incidence is higher in individuals with inflammatory bowel disease (IBD) (Peter et al., 2018), and this risk increases by 30% in ulcerative colitis patients. This review highlights the link between Hcy and PD pathogenesis based on the origin of Hcy and the mechanism between HHcy and GIT dysfunction in PD. Furthermore, this investigation aims to elucidate the association of HHcy in the progression of GIT symptoms in PD, providing the foundation for strategies to control Hcy levels during PD treatment.

2. Origins of Homocysteine

2.1 Homocysteine undergoes metabolism in the body via various mechanisms

There are three metabolic pathways of Hcy in the body: (1) Hcy remethylates to Met, where 5-methyl tetrahydrofolate (5-MTHF) serves as the methyl donor under the action of 5,10-methylene tetrahydrofolate reductase (MTHFR). Met synthase (MS) transfers a methyl group from MTHF to Hcy when MTHF converts to tetrahydrofolate (THF). This pathway is called the folate-dependent Met cycle and occurs in all the organs. (2) The transsulfuration pathway, where Hcy is metabolized to cysteine and α-ketobutyric acid via cystathionine β-synthase (CBS) and cystathionine γ-lyase (CGL) permanently. This pathway is mediated by vitamin B6 (pyridoxine) and occurs in the kidney, liver (Karmin & Siow, 2018), and brain. (3) Hcy is catalyzed to homocysteine thiolactone (HTL) by Met-tRNA synthetase (MARS), and the process occurs in various organs in the body. HTL links with lysine residues in the protein, causing N-homocysteinylation, thereby altering the conformation and function of these proteins (Jakubowski, 1999). (4) There exists an additional pathway that does not rely on folate. The Betane acts as a methyl donor to facilitate the conversion of Hcy to Met through the action of Betaine-homocysteine methyltransferase (BHMT), which is primarily found in the liver (Alirezaei, 2015) (Figuer 1).



Figuer1: Homocysteine metabolism(Created with BioRender.com). BHMT, Betaine-homocysteine methyltransferase; MS, Met synthase; MTHFR, 5,10-methylene tetrahydrofolate reductase; 5-MTHF, 5-methyl tetrahydrofolate; THF, tetrahydrofolate; B12, vitamin B12; MARS, Methionine-tRNA synthetase; HTL, homocysteine thiolactone; CBS, cystathionine β-synthase; CGL, cystathionine γ-lyase; B6, vitamin B6; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; Hcy, homocysteine; Met, methionine.

2.2 Hyperhomocysteinemia in PD arises due to various factors

Levodopa was discovered in the 1960s and was the first symptomatic treatment for PD. However, this treatment elevates circulation Hcy levels as levodopa is metabolized via catechol-O-methyltransferase (COMT), and SAM is the methyl-group donor to catalyze Hcy products (O'Suilleabhain et al., 2004). When compared with levodopa-naive PD patients or healthy controls, patients with prolonged levodopa therapy had 30 - 80% elevated Hcy levels. Nutritional deficiencies such as vitamin B6, folate, or B12 can cause HHcy (Al-Kuraishy et al., 2023). Since motor symptoms may progress into impaired self-care and dysphagia, malnutrition is frequently observed in late PD stages, with a prevalence of 24%.. Furthermore, about 60% of PD patients, such as vitamin B deficiency, are at risk of malnutrition Moreover, levodopa metabolism also demands vitamin B, which may lead to Hcy depletion (44). In late PD stages, abnormal intestinal absorption of vitamins is also observed in levodopa/carbidopa intestinal gel (LCIG) recipients. Generally, there is an age-related increase in plasma Hcy level (Xu et al., 2020), which might be caused by deficiencies of vitamin B6, folate, and vitamin B12 or because of kidney impairment and decreased activity of Hcy-eliminating enzymes. Furthermore, the plasma levels of Hcy in men are often higher than in same-age women (Verhoef et al., 1999), which might be because men have fat-free mass, explained by different levels of creatinine clearance and estradiol pathways. The elevated fasting Hcy during menopause was linked with a lack of estradiol. It has also been observed that Hcy is reduced after hormone replacement therapy starts in postmenopausal women, which might be associated with the activity of Met synthase (Mijatovic et al., 1998). Monika et al. reported that Hcy levels were markedly elevated in PD patients than in controls and were substantially linked to MTHFR 677 > T polymorphism both in PD patients and controls, where T allele carriers indicated notably increased Hcy plasma levels. Levodopa is converted to 3-O-methyldopa and dopamine by COMT and requires SAM as a methyl donor. Mutations in MTHFR genes can reduce MTHFR antivity, leading to further Hcy metabolism disorders (Religa et al., 2006).

Congenital HHcy caused by a deficiency of Met synthase is hereditary. Furthermore, it has been suggested that environmental factors are primarily responsible for increased Hcy in PD patients undergoing levodopa therapy. In a controlled study, there was no significant difference in Hcy between the non-treated PD patients and control groups. Hcy levels were significantly highly in levodopa-treated PD patients compared with non-treated PD patients and controls particularly in the case of MTHFR 677T/T and C/T type variations. Therefore, although nutritional deficiencies, age, gender and genetic factors are major modifiers of the degree of increase, it seems that therapy with levodopa is the major culprit (Postuma & Lang, 2004).

3. Hyperhomocysteinemia and Intestinal Disease

The literature has indicated that ulcerative colitis is associated with increased tHcy levels, particularly in the active and relapsing stages, which appear unaffected by normal folate status and which may contribute to a procoagulant blood profile (Drzewoski et al., 2006). The other study, patients with ulcerative colitis and Crohn's disease had significant elevated levels of Hcy in the colonic mucosa. A comparative study analyzed 138 healthy persons and 65 individuals with IBD. Compared with control group, Hyperhomocysteinemia is significantly more common in patients with IBD (Romagnuolo et al., 2001). As a result, additional investigation is required to explore the contribution of GIT tissue in the overall production of net Hcy and its interaction with the gut. In this discussion, we will examine some significant discoveries(ZHANG et al., 2023).

3.1 Role of Hyperhomocysteinemia in the intestinal barrier

The intestinal barrier comprises epithelial cells and the apical junctional complex, which acts as a physical barrier to prevent the penetration of hazardous substances into the intestinal mucosa. The main component of the barrier is the junction that acts as an effective barrier, blocking the entry of microorganisms, microbiome toxins, antigens, digestive enzymes, and other harmful substances from the GIT to the internal environment. The primary transmembrane proteins that link the junctional complex with cytoskeletal proteins are claudins, occludin, and ZO-1 (Vaziri et al., 2012). A single Met dose of 100 mg/Kg body weight in humans can elevate plasma Hcy content. Met, the primary source of Hcy, is mainly acquired from food. Several researchers have induced HHcy in experimental animals via a high Met diet (Azad et al., 2018). Recently, a study utilized the isotope-labeling method in piglets, indicating that GIT tissue metabolizes 20% of the dietary Met into Hcy (31%) (Riedijk et al., 2007). Prior research has shown that the GIT metabolizes 20% of ingested methionine to produce Hcy (62). A mouse model of hyperhomocysteinemia-uremia shows that hyperhomocysteinemia can worsen the increase in permeability of the intestinal epithelium and dysfunction of tight junctions by reducing levels of claudin-1, occludin, and ZO-1 through inflammation and oxidative damage, such as increasing levels of interleukin-6(IL-6), tumor necrosis factor-α (TNF-α), and malondialdehyde (MDA), and decreasing levels of superoxide dismutase (SOD). In a rat model of trinitrobenzene sulfonic acid (TNBS)-induced colitis, the injection of Hcy resulted in a more pronounced increase in intestinal epithelial permeability, as examined through Evans blue (EB) dye (Ding et al., 2014). The maternal separation model demonstrated that Hcy caused an increase in intestinal paracellular permeability by disrupting the occludin protein, which is responsible for maintaining tight junctions (TJs) in the cell membrane. However, treatment to lower Hcy levels restored the integrity of TJs. The expression of tight junction proteins ZO-1, occludin, and claudin-1 was reduced in Caco-2 cells following homocysteine thiolactone(HT) treatment. In

addition, Hcy is known to cause damage to the intestinal barrier by affecting the occluding, claudin-1, and ZO-1 junctions in individuals with chronic renal disease. This is achieved by lowering the hypoxia-inducible factor-1α (HIF-1α) levels and microRNA-223. Furthermore, HHcy exacerbates constipation (Givvimani et al., 2012). Additional studies are required, although observational and experimental studies prove that HHcy enhances intestinal barrier function.

3.2 Hyperhomocysteinemia may exacerbate Intestinal inflammation

The primary purpose of the intestine is to facilitate the process of digestion and absorption of nutrients. Clinical investigations have shown that lymphoid tissues have a more significant concentration of lymphocytes than other tissues. These lymphocytes are crucial in protecting the gastrointestinal mucosa as immunological barriers. Lymph nodes are capable of withstanding the harmful effects of pathogenic antigens through both humoral and cellular immunity. They serve as crucial locations for the body's immunological defense mechanisms. Homocysteine can compromise the immune system's ability to defend against external pathogens and mitigate intestinal inflammation by modulating the levels of pro-inflammatory and anti-inflammatory proteins within the body. A study has shown that levels of Hcy are increased in the plasma and mucosa of patients with IBD. Additionally, Hcy increases inflammation in the mucosal endothelium, leading to increased levels of TNF-α and vascular cellular adhesion molecule-1(VCAM-1), as well as enhanced production of monocyte chemoattractant protein-1 (MCP-1). Notably, a genetic colitis model lacking interleukin-10(IL-10) showed that Hcy levels may exacerbate colonic inflammation due to the absence of hydrogen sulfide (H2S) generation (Flannigan et al., 2014). Hcy exhibited a dose-dependent effect in promoting the development of CD4 T cells into Th17 cells. Th17 cells triggered by the activity of IL-6 and transforming growth factor β (TGF-β) can secrete large amounts of IL-17A and express the transcription factor retinoic acid-related orphan receptor gamma-T (RORγt), especially can boost other immune cells such as Th1 cells and neutrophils (Wiche Salinas et al., 2021). Th17 cells are considered as driving autoinflammation by producing a unique set of cytokines such as IL-17A, IL-21, IL-6, and interferon-γ (IFN-γ). In addition, HHcy elevates the susceptibility to IBD by inducing oxidative damage to the colon tissue (Chen et al., 2012). And thromboembolic which seems to link with HHcy represents an important cause of morbidity and mortality in patients with inflammatory bowel disease. Homocysteine can increase the production of many pro-inflammatory substances, including TNF-α, IL-6, IL-1β, and IFN-γ. These proteins, in turn, can negatively impact the intestinal mucosa and increase its permeability through the tight junctions between cells (Ding et al., 2014). During the cellular study,Caco-2 cells mRNAexpression of inflammatory cytokines IL-1β, IL-6, and TNF-α increased after HT treatment that HT is a cyclic thioester of homocysteine (Duan et al., 2023).the application of fucose has been found to modify the metabolism of Fusobacterium nucleatum. This

alteration leads to a decrease in homocysteine thiolactone (HT), a cyclic thioester of homocysteine. As a result, there is an increase in the mRNA expression of inflammatory cytokines IL-1β, IL-6, and TNF-α in Caco-2 cells Therefore, substantial evidence supports the connection between an inflammatory state and HHcy in intestinal disease. This shows that Hcy may impact the intestines' compromised health by exacerbating inflammation.

3.3 Hyperhomocysteinemia is involved in intestinal microvascular

HHcy has been linked to intestinal microvascular dysfunction, intestinal barrier, and inflammation. Bowel disease is a long-lasting inflammatory condition affecting small and large blood vessels. Simultaneously, certain studies have shown that microvascular dysfunction leads to stubborn inflammatory ulcerations in the intestine due to reduced ability to dilate blood vessels and inadequate blood flow in the gut (Peyrin-Biroulet et al., 2007). Furthermore, Hcy can enhance the inflammatory response of intestinal microvascular endothelial cells in vitro. When There is a microcirculation disorder in the intestinal mucosa, the blood supply to the intestinal mucosa is insufficient. This can lead to damage to the integrity of the intestinal mucosa, which in turn increases the permeability of the intestinal mucosa. As a result, the selective permeation and barrier function of the intestinal mucosa are weakened. Empirical research has demonstrated that TNF-α, IL-6, and other inflammatory agents can enhance the permeability of vascular endothelial cells and compromise the integrity of the intestinal mucosal barrier (Che et al., 2022). Hcy induced enhanced permeability of human intestinal microvascular endothelial cells through both paracellular and transcellular transport mechanisms, including the degradation of vascular endothelial cadherin and zona occludens-1, as well as the development of caveolae.

A case-control study on 174 IBD patients and 273 healthy controls revealed that IBD patients had elevated serum Hcy levels, increased risk of developing colon cancer, and the incidence of thromboembolic complications. Moreover, it was also revealed that HHcy increases the risk for thromboembolic events in pediatric IBD (Dilillo et al., 2022). Overall, this evidence indicates a connection between HHcy and the occurrence of intestinal problems through multiple causes.

4. Pathologic Theory of the Intestinal Origin of PD

4.1 Abnormal α-synuclein aggregation linked to PD

The identified pathology is linked to the degradation of neurons and the accumulation of α-synuclein protein aggregates in the neurons of the SN. These aggregates are known as Lewy bodies and Lewy neurites. α-synuclein is highly prevalent in the brain, particularly in synaptic terminals, and plays a crucial role in the transit of vesicles and neurotransmitters. Pathogenic mutations of α-

synuclein can cause the rapid development of aggregates that can capture organelles, including mitochondria and lysosomes (82) mitochondrial dynamics including mitochondrial fission, fusion, transport and so on and may disrupt mitochondiral protein import mechanisms (Rocha et al., 2018). Currently, non-motor symptoms are highly apparent in PD, and the presence of GIT symptoms may arise before the motor symptoms caused by the substantia nigra for several decades. Autopsy examinations revealed the presence of Lewy bodies and neurites in the ENS of 10 PD individuals92 individuals(83). Furthermore, the atypical accumulation of α-synuclein in the peripheral nerves of the intestines may be the primary factor responsible for constipation in clinical settings (Challis et al., 2020). The buildup of α-synuclein at the molecular level may be associated with a cascade reaction that disrupts the balance of inter-organellar homeostasis, including decreased mitochondrial activity. According to Braak's idea, it is suggested that the usual disease process may start in the GIT and subsequently extend to the brain through the vagus nerve (Braak et al., 2006). However, it is still debated. Recent findings by Marie et al. suggest that α-synuclein is distributed by a potential systemin mechanism, where the general circulation serves as a pathway for long-distance bidirectional transmission between the ENS and CNS (Arotcarena et al., 2020). In summary, protein aggregation is closely linked to the gut. However, further extensive studies are required.

4.2 The gut microbiome, intestinal permeability, peripheral inflammation, and neuron inflammation affect PD

PD is regarded as a multi-system disease with significant immunological dysfunction and neuroinflammation that has been linked to the emergence of several non-motor symptoms, including fatigue and GIT dysfunction. When reactive microglia were discovered in postmortem PD patient tissue in 1988, McGeer et al. established a connection between neuroinflammation and PD (Tansey et al., 2022). Activated microglia contribute to the elevation of TNF, IL-1β, TGFβ, IL-6, reactive oxygen species (ROS), nitric oxide species, and pro-apoptotic proteins in the substantia nigra pars compacta, striatum, and cerebrospinal fluid (CSF) of individuals with PD. Surprisingly, α-synuclein may exhibit an positive association with inflammation. Fibrillar α-synuclein can activate inflammatory pathways in monocytes, producing IL-1β through toll-like receptors. In contrast, data indicates that inflammation associated with infection stimulates enhanced α-synuclein expression in living organisms. A clinical observation revealed that norovirus infection in the human gastrointestinal system caused an increase in the expression of α-synuclein.

Nevertheless, immune activation plays multiple roles and may provide advantages, especially in the initial phases of neurodegeneration, by facilitating the removal of aberrant protein aggregates. The malfunction of immune-mediated clearance processes may eventually lead to the buildup of

aggregates. However, the exact transition of this state of balance from being protective to becoming toxic is still not completely understood (Weiss et al., 2022). The intestine serves as the primary connection point between the internal body and the exterior environment, and it is significantly affected by the microbiome. It is commonly known that the gut microbiota of people with PD differs from that of controls. High levels of gut inflammation in PD are also associated with microbiome diversity. A meta analysis about the link of gut microbiota and PD showed significantly lower abundance of *Prevotellaceae*, *Faecalibacterium*, and *Lachnospiraceae* from PD patients (Shen et al., 2021). Members of the *Prevotellaceae* family are reduced in patients with PD, which could lead to a reduction in the synthesis of mucin in the intestinal mucosal layer. The reduction in mucin favours the aggregation of α-synuclein in the colon and brain by increasing intestinal permeability, which facilitates the entry of bacterial toxins and antigens. The dysfunction of the intestinal barrier also allows the passage of bacteria and bacterial products such as lipopolysaccharides(LPS). Toll-like receptors (TLRs) are pattern recognition receptors that are expressed throghout the gastrointestinal tract in intestinal epithelial cells and in various immune cells. In the vasculature, LPS induces the activation of various immune cells, resulting in production of inflammatory cytokines that enter the brain though blood-brain barrier. Microglial TLRs can also be activated by LPS, which leads to increased expression of pro-inflammatory cytokine, costimulatory molecules and major histocompatibility complex classII (Li et al., 2021). A study about PD mouse showed that *Prevotella* can produce hydrogen sulfide to protect dopaminergicneurons (Bullich et al., 2019). According to a nonparametric meta-analysis of PD patients across five different countries, there is a decrease in short-chain fatty acids (SCFA) and an increase in *Akkermansia* (Hirayama & Ohno, 2021). SCFA are produced by *Lachnospiraceae*, *Roseburia*, *Faecalibacterium* and *Blautia* which were decreased in PD patients and have a role in maintaining homeostasis and regulating the turnover of the gut epithelium.

The reduction of SCFA also may influence intestinal α-synuclein. SCFs like butyrate can reduce reactive oxygen species which promote α-synuclein accumulation in the colon to regulate colonic mucosal oxidative stress. An experimental investigation has shown that mice exhibited increased microglia activation and a-synuclein accumulation after receiving fecal microbiota from patients with PD via oral gavage (Sampson et al., 2016). Microbiota dysbiosis can cause damage to the intestinal barrier, also known as "leaky gut," which speeds up the unchecked passage of bacterial components, byproducts of bacterial metabolism, and hazardous substances, including inflammation factors. This can cause inflammation in the bloodstream and brain, affecting the gut-brain axis. The exact mechanisms by which the gut microbiome and other metabolic processes may contribute to the stimulation or progression of PD are currently unknown and are the subject of ongoing investigation.

5. A Potential Pathway Linking Hyperhomocysteinemia and Gut-Brain Disorder

Moreover, there is a significant correlation between HHcy and vascular dementia, AD, PD, and other neurodegenerative disorders. The literature has indicated that HHcy is an independent risk factor for PD development (Aborode et al., 2022). Furthermore, the total Hcy level of PD patients is higher than that of healthy controls. A prospective study comprising 456 untreated PD patients recently indicated that increased Hcy levels were linked with worse baseline MMSE scores and more significant annualized decline MMSE (Christine et al., 2018). Moreover, elevated concentrations of Hcy in PD patients shows severe peripheral neuropathy, cognitive decline, hallucinations, increases the risk of cardiovascular disease. Importantly, there is a correlation between plasma Hcy levels and both motor symptoms and non-manifestations in PD. Hcy significantly affects the neural system via communication between the central and enteric nervous systems, known as the gut-brain axis. The relationship between HHcy and PD is intricate, potentially leading to several pathological changes that contribute to the development and progression of PD. Homocysteine plays a role in the N-Methyl-D-aspartic acid(NMDA) receptor directly or inhibits γ-aminobutyric acid (GABA) indirectly, resulting in neuronal Ca2+ overloads and excitotoxicity. A previous study showed that glutamate-mediated excitotoxicity is linked with dopaminergic neuron loss in PD (Muddapu et al., 2019). Furthermore, in PD, GABA can reduce motor and non-motor symptoms such as sleep disorders. A cross-sectional study demonstrated that elevation of plasma Hcy was associated with PD accompanied by minor hallucinations, which probably decreases NO and increases ROS, thereby promoting immune cascade reactions and damaging specific brain neurons such as those in the default mode network (Zhong et al., 2022). In the same study, the researcher was evaluated by NMS and found that elevated Hcy positively correlated with GIT, implying that Hcy influences non-motor symptoms in PD patients. Moreover, HHcy decreases intestinal motility (constipation) by inducing inflammatory changes such as elevation of matrix metalloproteinase-9(MMP-9) expression in mice. These data suggest possible links between HHcy, GIT, and the development/progression of PD.

5.1 Hyperhomocystiene-induced intestinal flora disorders

Intestinal flora disorders are strongly associated with intestinal diseases and GIT dysfunction in PD. It has been known that gut microbiota constitutes an integral part of the body, and its disorders, called dysbiosis, are observed in various systems and organ pathologies. The risk of IBD incidence increases with intestinal dysbiosis, which damages tight intercellular connections and increases intestinal permeability, which enhances the absorption of endotoxins (particularly lipopolysaccharide). Therefore, the endotoxins can enter the systemic circulation and cause chronic systemic inflammation. An integrative

correlation network generated by metagenomics and serum metabolomics revealed that microbial capability contributes to Hcy in PD patients (Rosario et al., 2021). It has been shown that *a. muciniphila*, *Eubacterium sp.*, *Subdoligranulum sp.*, and *Clostridiales family XIII* were identified as the primary Hcy producers and were more enriched in PD patients than controls based on the personalized community metabolic modeling. The enrichment of *A. muciniphila* occurred in PD patients and also was found in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced PD mice models. Mucin degradation through *A. muciniphila* can damage intestinal inflammation and barrier, leading to circulation inflammation but compensatory increase in mucus synthesis conversely resulted in anti-inflammation effects in the host that may explain *A. muciniphila* was found in excessive amounts in PD as probiotic. Consistently, a mice experiment showed that oral administration *A. muciniphila* without mucin cultivation could lead to α-syn aggregation. However, whether *A. muciniphila* is involved in production of Hcy needs to be further explored. According to a mendilian randomization, high levels of *Eubacterium sp* correlated with increased PD risk (Jiang et al., 2023). While in a randomized controlled study, after probiotics treatment, PD patients occurred *Eubacterium sp* decreased (Du et al., 2022). A rheumatoid arthritis mice models showed *Subdoligranulum* stimulated TH17cells and systemic autoantibody generation but how it involved in PD is unknown so far. A polyriboinosinic-polyribocytidylic induced schizophrenia mice models showed abundance of *Clostridiales family XIII* was increased that associated with the tremendous activation of the immune system and a strong increase in microglial cells. These findings suggest that Hcy has a strong link with the gut, though that remains unclear, and the microbiome may play a significant role (Chen et al., 2010). In the research about Hcy, *Dubosiella* increased in HHcy animal models, and Hcy was detected in *Dubosiella* newyorkensis-cultured supernatant. Furthermore, Hcy animal models indicated increased Hcy-related KEGG orthologies (KOs). Moreover, *Dubosiella* was positively associated with the p-α-Syn/α-Syn ratio in the brain and colon of PD mice after MPTP administration. This suggests that *Dubosiella* may contribute to the acceleration of PD through the production of Hcy. However, a previous study on PD mice showed that plasma Hcy was not elevated after 5 days of MPTP injection (Bhattacharjee et al., 2016). This implies that high Met dietary intake may contribute to elevating Hcy. The findings indicate that Hcy is partially produced by GIT tissue. However, further investigation is required to understand the relationship between Hcy and the gut flora in individuals with PD. Furthermore, an elevated concentration of Hcy caused by a lack of vitamin B12 exacerbates imbalances in the gut microbiota and facilitates the proliferation of harmful microorganisms.

5.2 Hyperhomocysteine affects brain inflammation through intestinal permeability and inflammation

Numerous studies have proposed that PD has been shown to be

strongly associated with neuroinflammation and intestinal inflammation is involved via gut-brain axis. In various studies about tissue and animal models of PD, the activated microglia participated in neuroinflammation. Even activated microglia with over-expression of major histocompatibility complex (MHC)-II cell surface receptor was detected in SNpc of postmortem PD brains. The activated microglia also produced abundant inflammatory mediators such as TNF-α, IL-6, nitric oxide synthase-2 (NOS2), cyclooxygenase-2 (COX2), and ROS which mediated presentation of neoantigens to CD4+ T cells through MHC-II and eventually resulted in DA neurons death (Marogianni et al., 2020). A case-control study demonstrated that levels of proinflammatory cytokines (IL-6, TNF-α, and IL-1β) were substantially elevated in PD patients' colons (Devos et al., 2013) Zhao's study showed that rotenone-induced PD mice had increased TNF-α, IL-6, COX2, IL-1β, and NOS2 levels in the colon, circulation and brain (Zhao et al., 2021). Nevertheless, it's found that Hcy also increased intestinal permeability by reducing occluding, claudin-1, and ZO-1, as well as destroying the epithelial barrier by inducing inflammatory such as IL-1, IL-6, and TNF-α and oxidative damage (Liang et al., 2018). Accroding to previous literature, the more severe constipation seen in PD patients with HHcy may be related to Hcy-induced intestinal inflammation, which further exacerbates neuroinflammation through leaky gut and finally leads to DA neurons death. Another important immune cell that has been implicated in the pathogenesis of PD is Th17 cell. PD patient's colon biopsies have also revealed elevated expression of inflammatory markers, such as TLR-2, CD3+T cells, TLR4, T helper (Th) 1, Th17 and related proinflammatory chemokines and cytokines including TNF-α, IL-17A, IFN-β, IL-1β, IL-6, IL-8, IFN-γ, as well as glial cell markers. A research showed Th17 cells had direct neurotoxic effect that was increased in PD patients (Sommer et al., 2018). Evenly, the mice model without expression of IL17A occurred that brain barrier disruption, motor disability and DA neuron loss were alleviated. Th 17 cells had been proved that inflammatory factors such as TNF-α, IL-1β, and IL-6 could activate Th17 cells and conversely Th17 cells secrete pro-inflammatory cytokines to promote inflammatory reactions and neuron death. On the other hand, the study about IBD mice models demonstrated that Hcy promoted CD4 T cells differentiation into Th17 cells and increased levels of IL-17 and RORγt (Gao et al., 2018). Furthermore, a previous study even showed HHcy increasing IL-17 levels via the p38/cPLA2/COX2/PGE2 signaling pathway (Zhu et al., 2015) HHcy may also exacerbate the PD intestinal immune-inflammatory reponse through activation of Th17 cells pathway. Simultaneously, HHcy activates NF-κB, thereby releasing pro-inflammatory cytokines. A study about PD mice induced by MPTP showed that the presence of proinflammatory M1 monocytes/macrophages and DAergic alterations in GIT are dependent on the MyD88/NF-κB signaling pathway, which produces proinflammatory cytokine and nitrite (Cote et al., 2015). IL-17 signaling also induces the activation of NF-κB cascade response to control the a part of physiological function. IL-17A also plays a phthogenic

role to stimulate glial cells and accelerate neuron inflammatory response in the CNS. Furthermore, HHcy triggers oxidative stress and inflammation via NF-κB signaling pathway activation. These studies imply that Hcy may worsen GIT dysfunction in PD patients with HHcy than in those without homocysteinemia by exacerbating intestinal inflammation(Figure2).

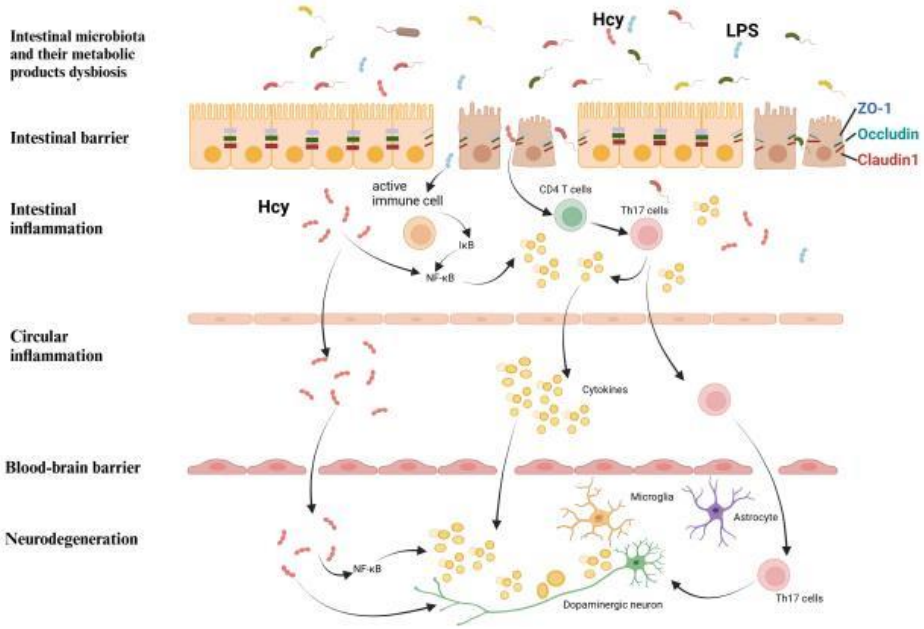


Figure 2: Schematic diagram of the positive effects of Hcy through the microbiota-gut-brain axis(Created with BioRender.com).

5.3 Hyperhomocysteine causes intestinal damage via gut microvascular

Hcy has many negative impacts on the vascular system as it destroys vessel wall integrity and, in turn, the vascular tone, resulting in vascular inflammation. Chen's study showed that high Hcy levels are associated with mesenteric microcirculation (Wang et al., 2020). Moreover, Hcy decreases nitrogen monoxide (NO), the most potent vasodilator secreted by the endothelium to induce endothelial dysfunction. Hcy inhibits NO release either by inhibiting NO synthase (eNOS), which supports the over-expression of caveolin-1 that binds the inactivated eNOS or by reducing the cationic amino acid transporter that provides arginine for NO synthesis. Moreover, sulfhydryl Hcy is oxidized easily to produce superoxide anion(O-2) species that interact with NO, quickly forming peroxynitrite (ONOO-) to compromise endothelial function and cause thromboxane A2 (TXA2), an arteriolar vasoconstrictor. Research revealed that intestinal epithelial isolated from the intestinal mucosa of IBD patients can enhance intestinal TXA2 synthesis (Zifroni et al., 1983). Hcy may block intestinal microcirculation by decreasing NO and increasing TXA2. Furthermore, endothelial cells with increased Hcy levels elevate tissue factor expression, such as factors V and XII, resulting in thrombin formation via a coagulation cascade. A case-control study revealed that plasma Hcy elevation

is linked with an elevated risk of acute mesenteric venous thrombosis (He et al., 2010). In addition, there is a correlation between Hcy and colitis due to its ability to promote mitochondrial fission, resulting in a lower ratio of mitochondrial fusion protein-2 (Mfn-2) to dynamin-related protein-1 (Drp-1) and subsequent mitophagy. This process damages endothelial cells and causes collagen accumulation in the mesenteric artery. HHcy can trigger an inflammatory reaction in intestinal microvascular endothelial cells, increasing VCAM-1 level, MCP-1 synthesis, and p38 phosphorylation. Therefore, Hcy can enhance the expression of chemokines, chemo-attractant proteins (MCP-1 and il-8), tissue factor, VCAM-1, and MMP-9, thus activating chemo-taxis of peripheral blood monocytes in humans. These results indicate that Hcy may impede intestinal function by influencing the development of microvascular lesions in the intestines, which may also contribute to PD's intestinal dysfunction.

5.4 Hyperhomocysteine sharpens abnormal α-synuclein aggregation

The Hcy metabolite, HTL, is a cyclic thioester with an esterified carboxyl group and strongly interacts with the ε-NH2 groups of the lysine residues of proteins, causing protein homocysteinylation, and alters the protein structure, activity, and function. The α-syn aggregation is essentially associated with PD pathogenesis. Research showed that HTL covalently modifies α-syn on the K80 residue, and the α-syn N-homocysteinylation promotes its accumulation and forms fibrils in the brain with elevated seeding activity and neurotoxicity such as decreasing motor deficits in a PD mouse model (Zhou et al., 2023). According to Braak's hypothesis, the gut microbial products interact with α-syn in enteric and olfactory neurons, triggering abnormal α-syn aggregation in the CNS via the vagus nerve and olfactory bulb, which eventually reaches the SNpc (Braak et al., 2003; Rietdijk et al., 2017). A hypothesis suggests that N-homocysteinylation of α-syn can build up in the gut, leading to gut dysfunction and exacerbating the accumulation of N-homocysteinylation of α-syn in the brain. However, further experimental and clinical biopsy certification is needed to confirm these outcomes. The Hcy appears to significantly interact with the nervous system through the gut-brain axis, a communication channel between the central and enteric nervous systems.

6. Conclusion

This study highlights the critical role of homocysteine (Hcy) and the gut-brain axis in the progression of Parkinson’s disease (PD) and their implications for neuromuscular function, physical activity, and rehabilitation outcomes. The findings suggest that hyperhomocysteinemia (HHcy) contributes to neuroinflammation, endothelial dysfunction, and gut microbiota dysbiosis, all of which accelerate dopaminergic neurodegeneration and motor impairment in PD patients. Given that physical activity and structured rehabilitation programs play a fundamental role in PD management, understanding the metabolic

disturbances associated with HHcy can help optimize exercise interventions, reduce fall risk, and improve neuromuscular adaptation.The gut-brain axis serves as a key mediator linking gastrointestinal dysfunction, inflammation, and α-synuclein pathology to the progression of motor and non-motor symptoms in PD. The interaction between HHcy and gut dysbiosis further exacerbates systemic inflammation, oxidative stress, and impaired neuromuscular coordination, potentially limiting the effectiveness of physical therapy and motor function rehabilitation strategies. This underscores the need for integrative treatment approaches that combine nutritional interventions, pharmacological therapies, and tailored exercise regimens to mitigate the detrimental effects of HHcy on both metabolic health and motor performance. From a sports and rehabilitation perspective, these findings emphasize the importance of early metabolic screening in PD patients to assess Hcy levels and gut microbiota composition, enabling personalized intervention plans that incorporate dietary modifications, targeted supplementation, and structured movement therapy. Given that regular physical activity is essential for maintaining motor function, postural stability, and muscular strength in PD patients, addressing HHcy-related impairments through lifestyle and exercise-based interventions can enhance functional independence and improve quality of life.Future research should focus on evaluating the long-term effects of exercise on HHcy levels, exploring how different training modalities influence metabolic resilience, and assessing the role of gut-targeted therapies in PD rehabilitation. Additionally, multidisciplinary studies integrating neurology, sports science, and nutrition will be crucial in developing comprehensive management strategies that support motor function, cognitive health, and metabolic stability in PD patients.By bridging the gap between metabolic dysregulation, neurodegeneration, and physical rehabilitation, this study provides valuable insights into how targeted interventions can improve exercise performance, neuromuscular adaptation, and overall well-being in individuals with PD. Addressing HHcy-related complications not only enhances the effectiveness of rehabilitation programs but also supports long-term mobility, independence, and participation in physical activity for PD patients.

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