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BEYOND THE BRAIN: THE GUT-LIVER-BRAIN AXIS AS A KEY PLAYER IN THE PATHOGENESIS OF PARKINSON DISEASE

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Abstract

History: Parkinson Disease is a slowly progressive neurodegenerative condition that is mainly marked by the loss of dopaminergic neurons and aggregation of α-synuclein. Historically viewed as a central nervous system condition, there is an increasing body of evidence to support the role of peripheral systems, especially gut–liver-brain axis, in its pathogenesis.

Purpose: The purpose of this review is to clarify the mechanistic action of the gut-liver-brain axis in PD focusing on gut microbiota dysbiosis, hepatotoxicity, and neuroinflammatory mechanisms.

Methods: An extensive review of the recent literature was performed in order to combine the results on microbial changes, liver dysfunction and their interplay on neurodegeneration.

Findings: Gut microbiota dysbiosis causes augmented intestinal permeability and endotoxin translocation (lipopolysaccharides), triggering systemic and hepatic inflammation. Hepatic dysfunction deteriorates the detoxification mechanisms leading to accumulation of neurotoxic metabolites such as ammonia and distorted bile acids. These factors disrupt blood–brain barrier integrity and activate microglia, promoting neuroinflammation, oxidative stress, and mitochondrial dysfunction. Moreover, mechanistic overlap of hepatic encephalopathy and PD illuminates common pathological processes comprising of neurotransmitter imbalance, astrocyte dysfunction, and dopaminergic deficits. The gut-liver-brain axis is therefore an important integrative pathway in the development of PD.

Conclusion: The gut-liver-brain axis is an important pathogenesis contributor of PD outside the brain. Microbiota modulation, hepatoprotective, and anti-inflammatory interventions have shown promising opportunities to target this tri-organ axis to achieve early diagnosis and disease modification.

Keywords: Parkinson’s disease, Gut–liver–brain axis, Gut microbiota, Neuroinflammation, Hepatotoxins, Hepatic encephalopathy, Oxidative stress, Dopaminergic neurodegeneration, Microglial activation, Dysbiosis

Introduction

Parkinson disease (PD) is a degree of non-progressive neurodegenerative disease, which is mainly associated with motor impairments caused by selective loss of dopaminergic neurons within the substantia nigra pars compacta and the occurrence of Lewy bodies that are primarily comprised of misfolded α-synuclein. The second most prevalent neurodegenerative disease is after the Alzheimer disease and has its motor and non-motor symptoms that severely worsen the quality of life (Kalia and Lang, 2015; Poewe et al., 2017).

Parkinson disease occurs in about 12-2% of the population above 60 years of age and the incidence of the disease rises significantly with age. Men are more influenced than women and it is possible that estrogen plays a protective role. There is geographic variation in prevalence and incidence of PD with higher rates reported in Europe and North America than in Asia and Africa. In India, the prevalence is estimated to be 70 to 328 per 100,000 population, but under-diagnosis is also a problem (Ascherio and Schwarzschild, 2016; Poewe et al., 2017). Parkinson disease etiology is multifactorial and complex in nature, with the interplay of genetic vulnerability and environmental exposures. The majority of the cases are sporadic, but about 5-10 percent of the cases are familial and associated with gene mutations like SNCA, LRRK2, PARKIN, PINK1 and DJ-1. PD has been highly linked with environmental risk determinants, such as being exposed to pesticides, herbicides, heavy metals, and neurotoxins like MPTP (Dauer and Przedborski, 2003; Ascherio and Schwarzschild, 2016).

Pathogenesis

The main pathophysiological process of PD is the gradual loss of dopaminergic cells in the substantia nigra causing the loss of dopamine in the striatum and impairment of basal ganglia circuits. The misfolded α-synuclein aggregation leads to the formation of Lewy bodies that induce the malfunctioning of synapses and death of neurons. According to Braak, α-synuclein pathology could start in the gut or olfactory bulb and infect the brain in a prion-like fashion (Braake et al., 2003; Kalia and Lang, 2015)Parkinson pathogenesis is complicated and includes several interconnected processes:

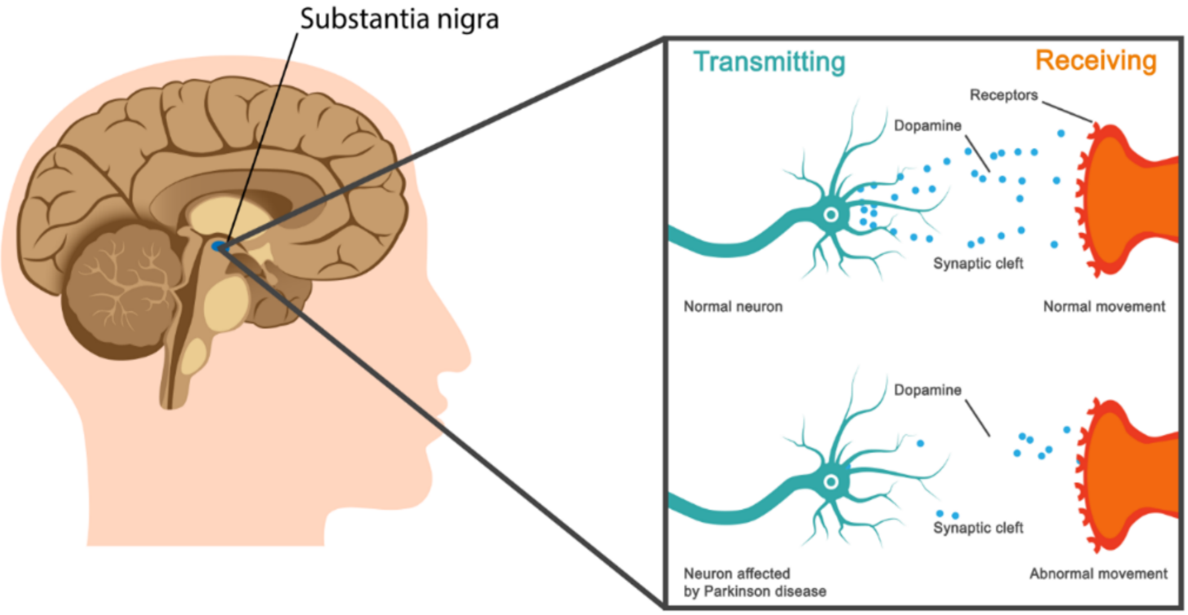

Fig no1: Development of Parkinson's disease

Source: https://www.porterhousemedical.com/news/parkinsons-disease-a-hopeful-future/

Hepatotoxins and Parkinson's Disease–Related Neuroinflammation

Hepatotoxins are chemical substances that damage the liver, resulting in poor detoxification and build-up of neurotoxic metabolites. Systemic inflammation, oxidative stress, and neuroinflammation, which hepatotoxins induce chronic liver dysfunction, are progressively known to contribute to the pathology of Parkinson's disease. The liver damage modulates the metabolism of ammonia, bile acid signalling, cytokine homeostasis and gut microbiota composition, which affect the gut-liver-brain axis. Microglial activation and dopaminergic neurodegeneration of susceptible brain areas like the substantia nigra pars compacta can be precipitated by these changes (Butterworth, 2013; Gore and Sheth, 2019; Bajaj et al., 2021).

Common Hepatotoxins Relevant to Neurodegeneration

Alcohol (Ethanol)

The long term effects of alcohol exposure include steatosis, hepatitis and cirrhosis resulting in hyperammonemia and systemic inflammation. Liver damage in alcoholism increases the pro-inflammatory cytokines (TNF-α, IL-1, IL-6) that may cross or disrupt the blood-brain barrier (BBB), triggering microglia and astrocytes. Another factor that improves oxidative stress and mitochondrial dysfunction, which play a role in dopaminergic neuron loss in PD, is alcohol (Crews and Vetreno, 2016; Qin et al., 2013.)

Carbon Tetrachloride (CCl_4)

CCl_4 is a classical experimental hepatotoxin that induces liver fibrosis via free radical–mediated lipid peroxidation. CCl_4-induced liver injury increases ammonia and inflammatory mediators, leading to neuroinflammation and cognitive–motor deficits. Microglial activation, astrocytosis, and a striatal decrease of dopamine levels revealed in rodent models recapitulate the features of Parkinsonism (Butterworth, 2013; Dhanda et al., 2019).

Acetaminophen (Paracetamol)

Acetaminophen overdose leads to acute liver failure which develops as a result of the production of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). Liver failure results in hyperammonemia, oxidative stress, and cerebral edema. These processes facilitate neuroinflammation and mitochondrial dysfunction, which are common with PD neurodegeneration.(Jaeschke et al., 2012; Butterworth, 2016)

Thioacetamide (TAA)

Thioacetamide is commonly employed in the production of hepatic encephalopathy in experimental models. Exposure to TAA causes astrocyte swelling, microglial activation and brain ammonia elevation. Such pathological processes are similar to neuroinflammatory processes in Parkinson disease (Norenberg et al., 2004; Rama Rao and Norenberg, 2014).

Mechanism of Hepatic Encephalopathy (HE)

Hepatic encephalopathy is a neuropsychiatric disorder resulting due to liver failure and loss of ammonia detoxification. High ammonia diffuses across the BBB, and is absorbed by the astrocytes, which transform it into glutamine, leading to osmotic stress, astrocyte oedema and cerebral edema. Ammonia also triggers mitochondrial dysfunction and oxidative stress and results in disturbed neurotransmission (GABAergic and glutamatergic imbalance). Moreover, systemic inflammation interacts with ammonia to stimulate microglia and promote neuroinflammation(Butterworth, 2013; Jalan et al., 2014).

Mechanistic Intersect with Hepatic Encephalopathy and Parkinson’s Disease.

Neuroinflammation

HE and PD are both typified by chronic neuroinflammation. Microglia are triggered by liver-derived cytokines and endotoxins in HE and misfolded α-synuclein in PD. Repeated microglial stimulation results in the susceptibility of dopaminergic neurons and a gradual neurodegeneration (Qin et al., 2013; Hirsch and Hunot, 2009).

Mitochondrial Dysfunction and Oxidative Stress.

In HE, hyperammonemia and PD, mitochondrial complex-I inhibition both lead to overproduction of reactive oxygen species (ROS). Dopaminergic neurons are highly vulnerable to oxidative stress as they have a high metabolic rate and their auto-oxidation of dopamine is highly active (Dias et al., 2013; Butterworth, 2016).

Dopaminergic Dysfunction

Chronic liver disease patients often have extrapyramidal symptoms that are similar to those of Parkinsonism. Impaired biliary excretion and alteration of dopamine receptor signaling leads to manganese build-up that is associated with basal ganglia dysfunction, thus directly correlating hepatic failure with Parkinsonian motor symptoms (Butterworth, 2010; Guilarte, 2013).

GutLiverBrain Axis: An Integrating Pathological Connection.

Hepatotoxins interfere with gut barrier homeostasis and change gut microbiota structure, augmenting endotoxin (LPS) transport into the bloodstream. LPS brings about hepatic and systemic inflammation, which in turn causes neuroinflammation. Gut dysbiosis is a precedent to motor symptoms in PD and plays a role in the aggregation of α-synuclein. So, gut dysbiosis caused by hepatotoxins offers a mechanistic linkage between pathology of HE and PD(Bajaj et al., 2021; Cryan et al., 2019).

Gut Microbiota in Parkinson’s Disease

This paper will review Gut Microbiota and Parkinson disease.

Human gut microbiota comprise trillions of microorganisms which are important in digestion, immune regulation, metabolism and neurodevelopment. The growing evidence indicates that gut microbiota composition changes (dysbiosis) play a role in the pathogenesis of the Parkinson’s disease (PD) via gut to the brain axis mechanisms. GIT symptoms including constipation normally have a lead time of several years on motor symptoms of PD, and gut pathology can be an initial stage in disease development (Cryan et al., 2019; Scheperjans et al., 2015).

2. Normal Gut Microbiota Composition.

2.1 Phyla in Healthy People.

The gut microbiota of healthy adults consists of four large bacterial phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Firmicutes and Bacteroidetes comprise around 90% of the total gut microbes. These bacteria play a crucial role in short-chain fatty acid (SCFA) synthesis, intestinal barrier stability, and immune homeostasis(Qin et al., 2010; Thursby & Juge, 2017).

2.2 The beneficial genera found in the normal gut microbiota include:

The valuable genera to include are Lactobacillus, Bifidobacterium, Faecalibacterium, Roseburia, and Prevotella. These microbes generate SCFAs including butyrate, acetate, and propionate that have anti-inflammatory effects, nourish colonocytes and preserve gut barrier functionality. Butyrate-producing bacteria especially Faecalibacterium prausnitzii play an important role in curbing intestinal and systemic inflammation (Louis et al., 2017).

3. Gut Microbiota Alterations in Parkinson’s Disease

3.1 Dysbiosis in PD.

There are substantial changes in the composition of gut microbes among patients with Parkinson disease and healthy people. The dysbiosis related to PD is characterized by a decrease in the microbial diversity and the transition to pro-inflammatory microbial populations. The changes are associated with the severity of the disease, motor symptoms, and non-motor gastrointestinal dysfunctions (Scheperjans et al., 2015; Bedarf et al., 2017).

3.2 Wasting Away of Beneficial Bacteria.

A number of studies have shown the decrease of Prevotella, Faecalibacterium and Roseburia in PD patients. Prevotella loss is related to reduced mucin production and enhanced intestinal permeability (leaky gut) to promote endotoxin translocation of lipopolysaccharide (LPS). Limited SCFA synthesis is a factor that leads to a poor gut barrier and an increase in neuroinflammation(Scheperjans et al., 2015; Unger et al., 2016).

3.3 Enrichment of Pathogenic and Pro-Inflammatory Bacteria.

Conversely, the PD patients exhibit a greater proliferation of the families of Enterobacteriaceae, Proteobacteria and Desulfovibrio. The bacteria generate endotoxins and hydrogen sulfide that cause oxidative stress and inflammation. The high levels of Enterobacteriaceae have been positively linked to postural instability and gait difficulty in PD patients (Keshavarzian et al., 2015; Shin et al., 2020).

Feature	Normal Gut Microbiota	Parkinson’s Disease
Microbial diversity	High and stable	Reduced diversity
Dominant phyla	Firmicutes, Bacteroidetes	Increased Proteobacteria
Short chain fatty acids (SCFA)-producing bacteria	Abundant (Faecalibacterium, Roseburia)	Reduced
Prevotella	Normal abundance	Markedly reduced

Enterobacteriaceae	Low abundance	Increased
Inflammatory status	Anti-inflammatory	Pro-inflammatory
Gut barrier integrity	Intact	Increased permeability

Table no 1 : Comparison of Normal vs Parkinson's Disease Gut Microbiota

Source : (Scheperjans et al., 2015; Cryan et al., 2019).

Mechanism of the Gut–Liver–Brain Axis in Neuroinflammation and Neurodegeneration

1. Concept of the Gut–Liver–Brain Axis

The gut–liver–brain axis is a bidirectional communication system integrating neural, immune, metabolic, and microbial pathways. Signals originating from the gut microbiota reach the liver through the portal circulation and influence hepatic metabolism, immune responses, and detoxification. In turn, liver-derived metabolites, bile acids, and inflammatory mediators affect gut microbial composition and brain function. Disruption of this axis is increasingly implicated in neurodegenerative disorders, including Parkinson's disease and hepatic encephalopathy .(Tripathi et al., 2018; Cryan et al., 2019; Bajaj et al., 2021).

2. Aggressive and Defensive Factors in the Gut–Liver–Brain Axis

2.1 Aggressive Factors

Aggressive factors are pathological stimuli that promote inflammation and tissue damage within the gut–liver–brain axis. These include pathogenic gut bacteria, endotoxins such as lipopolysaccharide (LPS), ammonia, reactive oxygen species, and pro-inflammatory cytokines. When produced in excess or inadequately cleared by the liver, these factors initiate systemic inflammation and act as potent triggers for neuroinflammatory cascades. (Tilg et al., 2016; Butterworth, 2013; Qin et al., 2013)

2.2 Defensive Factors

Defensive factors counterbalance inflammatory stimuli and preserve homeostasis. These include beneficial gut microbiota, short-chain fatty acids, intact intestinal tight junctions, effective hepatic detoxification mechanisms, anti-inflammatory cytokines, and a functional blood–brain barrier. Loss or weakening of these defensive mechanisms allows aggressive factors to dominate, leading to disease progression along the gut–liver–brain axis.(Thursby & Juge, 2017; Cryan et al., 2019; Braniste et al., 2014).

3. Liver Dysfunction in the Onset of Gut Dysbiosis.

3.1 Physiological Functions of the Liver in Gut Microbial Homeostasis.

In an ideal environment, the liver is a key controller of microbial balance in the gut via the portal circulation, bile acid secretion, immune control, and detoxification. The gut-derived microbial metabolites, endotoxins and antigens get into the liver through the portal vein and are cleared by hepatocytes and Kupffer cells. This stringent control stops overactive immune responses and a stable gut microbial ecosystem. The homeostatic mechanisms are disturbed by liver impairment and predispose to gut dysbiosis(Albillos et al., 2014; Tripathi et al., 2018)

3.2 Disrupted Bile Acid Metabolism and Microbial Shifts.

Liver-produced bile acids are not only necessary in the digestion of lipids but also serve as signaling molecules to control the composition of gut microbiota. Primary bile acids have antimicrobial activity and prevent the growth of pathogenic bacteria. The impairment of liver changes the bile acid synthesis, conjugation and the circulation of hepatocytes, resulting in the diminished antimicrobial pressure of the intestine. It selects in favor of the growth of deleterious taxa like Enterobacteriaceae and Proteobacteria and against advantageous commensals like Firmicutes, which causes dysbiosis (Ridlon et al., 2014; Tilg et al., 2016).

3.3 Decreased Hepatic clearance of Endotoxins and Microbial Metabolites.

The ability of the liver to detoxify endotoxins produced by gut including lipopolysaccharide (LPS), ammonia and bacterial metabolites is dramatically decreased in liver dysfunction. All these toxicants are deposited in the portal and systemic circulation, which produces the pro-inflammatory environment in the gut. Increased levels of endotoxins also disruptions of the gut epithelial activity and selective enhancements of inflammation-related microbial species, which reinforce dysbiosis. (Butterworth, 2013; Jalan et al., 2014).

3.4 Portal Hypertension and Intestinal Structural Changes

Portal hypertension is often connected with chronic liver disease, resulting in intestinal congestion, edema, and hypoxia. Such structural and vascular alterations deteriorate epithelial turnover and nutrient uptake, transforming the gut microenvironment. These circumstances support the growth of pathogenic bacteria and decrease the diversity of microbes, which are major contributors to dysbiosis in cirrhosis and liver failure (Assimakopoulos et al., 2018; Bajaj et al., 2021).

3.5 Greater Intestinal Permeability (“Leaky Gut”)

Disruption of tight junction proteins in the intestine, including occludin, claudins and zonula occludens-1 is linked with liver impairment. The impact of inflammatory mediators and oxidative stress undermines the integrity of the epithelial barrier, resulting in enhanced intestinal permeability. This permits bacterial translocation, and endotoxin entry into the circulation, which further destabilizes the gut microbial composition and continues dysbiosis(Assimakopoulos et al., 2018; Albillos et al., 2014).

3.6 Liver Disease Immune Dysregulation.

The liver is a key immunological organ which is tolerant to gut-derived antigens. Liver dysfunction modulates the innate immune response, especially the phagocytic activity and the pattern-recognition receptor signaling of Kupffer cells. This immune dysprocess results in insufficient microbial clearance and hyperinflammatory reactions in the gut, disrupting microbial homeostasis and promoting pathogenic species (Albillos et al., 2014; Tilg et al., 2016).

3.7 Disturbance of the Metabolism of Ammonia and Nitrogen.

Malfunction of the hepatic urea cycle causes hyperammonemia that directly impacts intestinal epithelial cells and changes the luminal pH. A high level of ammonia enhances the growth of bacteria that produce urease and thus ammonia is produced even further. This vicious cycle exacerbates gut dysbiosis and is part of the pathogenesis of hepatic encephalopathy (Butterworth, 2013; Norenberg et al., 2004).

3.8 Macrophages and Lymphocytes and the Development of a Vicious Cycle.

Liver impairment-induced gut dysbiosis enhances endotoxin translocation, which further exacerbates hepatic inflammation and fibrosis. This leads to a vicious cycle whereby dysfunction of the liver encourages dysbiosis and vice versa. The downstream effects of persistent systemic inflammation due to this cycle are apparent in distant organs, such as the brain.

(Tilg et al., 2016; Bajaj et al., 2021).

3.9. The pathological and neurological relevance can be found in liver

Liver impairment–induced gut dysbiosis plays a pivotal role in the gut–liver–brain axis. Amplified endotoxemia and ammonia play a part in neuroinflammation, microglial activation and dysfunction of neurons. These processes play a key role in hepatic encephalopathy, as well as neurodegenerative diseases, including Parkinson, in which chronic inflammation enhances the death of dopaminergic neurons (Butterworth, 2016; Cryan et al., 2019).

4. Neurodegeneration via the Gut–Liver–Brain Axis

Persistent neuroinflammation caused by gut dysbiosis and liver dysfunction leads to oxidative stress, mitochondrial dysfunction, impaired autophagy and synaptic dysfunction. There is a high susceptibility to dopaminergic neurons in the substantia nigra, which results in progressive neurodegradation and Parkinsonian motor symptoms.(Hirsch and Hunot, 2009; Dias et al., 2013)

5. Integrated Mechanistic Pathway

Liver impairment changes the bile acids metabolism and detoxification which causes gut dysbiosis and gut intestinal permeability. This enables the translocation of endotoxins and ammonia resulting in systemic inflammation, disruption of the blood-brain barrier, microglial stimulation, neuroinflammation, and eventual neurodegeneration.

(Butterworth, 2013; Cryan et al., 2019; Bajaj et al., 2021)

Future Scope

1.The Gut -Liver -Brain Axis: A Disease-Modifying Strategy.

Future studies are needed on therapeutic interventions that are able to concomitantly address gut microbiota, liver function, and neuroinflammatory pathways. Rather than considering

Parkinson's disease (PD) as a central nervous system disease, a systems-based approach, which incorporates peripheral contributors, including liver impairment and gut dysbiosis, can provide disease-modifying advantages.

2.Combined Hepatoprotective and Neuroprotective Therapies Development.

The range of agents of dual hepatoprotective and neuroprotective properties (e.g., agmatine, polyphenols, bile acid modulators) has a broad scope to be assessed. The endotoxemia, ammonia build up, and systemic inflammation could be decreased by such compounds, which indirectly counteract neurodegeneration.

3.Microbiota-Targeted Interventions

Future research ought to investigate probiotics, prebiotics, synbiotics, postbiotics, and fecal microbial transplantation (FMT) as possible methods to normalize gut microbial homeostasis in PD. Microbial signature-informed, personalized microbiome-based therapies could enhance the effectiveness of treatment and decrease disease progression.

4.Early Biomarkers and Predictive Diagnostics.

The composition of gut microbiota, bile acid, ammonia, and inflammatory mediators changes could be early biomarkers of Parkinson's disease. Longitudinal research is required to confirm these markers to diagnose at an early stage, predict outcome and assess treatment response.

5.Advanced Experimental Models

There is a necessity to design and optimize experimental models, which combine hepatotoxin-induced liver dysfunction with Parkinsonian neurodegeneration. These models will be more realistic in recreating clinical pathology and enhance translational relevance over traditional neurotoxin-only PD models.

6.Mechanistic Exploration of Immune Signaling Pathways

Future research might address important gut dysbiosis to neuroinflammation pathways, such as TLR4NF-KB signaling, NLRP3 inflammasome activation, microglial M1M2 polarization, and bloodbrainbarrier malfunction. These pathways could be targeted to offer new therapeutic targets.

7.Position of Diet and Lifestyle Modulation.

Non-pharmacological interventions (dietary) affecting the composition of the gut microbiota and liver health are a promising strategy. Systematic research of nutritional modulation, such as high-fiber diets, polyphenols and omega-3 fatty acids, should be conducted in the field of PD.

8.Translational and Clinical Studies.

Clinical trials should be well designed to apply the gut-liver-brain axis preclinical results in clinical practice. By combining gastroenterology, hepatology, and neurology in clinical research, the holistic management approach to Parkinson disease can be achieved.

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