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REVIEW ARTICLE

Cause or Effect? A Review of Evidence from the Past Two Decades Analyzing the Impact of Gut Dysbiosis on Parkinson's Disease

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ABSTRACT: The relationship between gut dysbiosis and Parkinson's disease has emerged as a focal point of scientific inquiries in the early 21st century due to a proliferation in knowledge surrounding the role of the gut-brain axis in neurological disorders. Over the last two decades in particular, evidence has suggested that the gut microbiota's release of pro-inflammatory cytokines, formation of alpha-synuclein, and decreased production of short-chain fatty acids (SCFAs)- whilst in a state of dysbiosis- have detrimental impacts on brain health, leading to profuse issues such as blood-brain barrier (BBB) permeability which catalyze Parkinson's disease. While many adopt this viewpoint, this topic remains contentious as numerous gut microbial researchers disagree with the notion that dysbiosis governs the disease, viewing it more as a consequence of Parkinson's ability to reduce motor integrity and alter lifestyle habits. This review aims to provide a nuanced resolution to the prevailing debate, analyzing research over the last 20 years to see whether the gut microbiota primarily causes Parkinson's disease or is just an effect of its modes of action.

KEYWORDS: Biomedical and Health Sciences, Pathophysiology, Neurodegeneration, Parkinson's Disease, Gut Dysbiosis.

Introduction

Parkinson's disease is widely regarded as one of the most significant medical and social burdens of our time, showing the fastest rising prevalence of all neurodegenerative diseases worldwide since being described over 200 years ago.[1] It is a chronic, progressive, and disabling disorder primarily troubling the elderly population and is expected to go from affecting 6.9 million individuals in 2015 to 14.2 million by 2040.[2] Parkinson's is caused by a significant loss of dopaminergic neurons in part of the brain called the substantia nigra, creating several motor and non-motor symptoms.[3] Historically, the disease was characterized by bradykinesia, a resting tremor, and difficulty walking; however, it is now evident that mood, hypotension, eye movement, and cognitive ability are also affected.[4] While these symptoms and the progression of the disease in general vary with each patient, the vast majority of cases are insidious in onset and advance slowly over time, making it difficult to diagnose early on.[5]

Since 1983, environmental factors and genetic changes have been known to play a big role in Parkinson's pathogenesis due to their relative ease of analysis. More specifically, exposure to farming chemicals like herbicides,[6] and having parents or siblings with the disease, makes individuals twice as likely to develop it themselves.[7] However, recent tests and findings from Parkinson's patients have unveiled a more surprising culprit, evoking the onset of the disease. The gut microbiome is prone to changes in both its composition and environment. This process is referred to as gut dysbiosis, which involves alterations to a diverse ecosystem of bacteria, Archaea, and Eukaryotes that colonize the gastrointestinal tract and interact with its host. The main causes of this imbalance in the gut are diet, such as having a high sugar or low fiber intake; xenobiotics, drugs, or food additives; and hygiene.[8]

Although the link between the host and the gut microbiota is mutually beneficial in healthy individuals, carrying out disease prevention and reducing inflammation,[9] dysbiosis has adverse effects, causing chronic inflammation, producing unwanted substances, and sending signals to the brain via the vagus nerve, which stimulates proteins and immune cells. The combination of these factors collaborates to significantly inhibit the functionality of dopamine-producing neurons, inevitably causing Parkinson's disease.[10]

While gut dysbiosis does evoke these problems, evidence from numerous fecal studies has made people consider an alternative approach: Parkinson's is a cause of gut microbial change rather than just a consequence.

So, in this review, we will go over the literature to answer the question of whether Parkinson's is predominantly an outcome or initiator of gut dysbiosis. The first part of this paper will provide evidence on how gut microbial change can cause the neurodegeneration that is characteristic of Parkinson's disease, while the second section of the paper delves into research surrounding the effects Parkinson's has on gut bacterial composition. These ideas will be followed by a discussion that evaluates the points stated and provides an opinion on which side of the argument is the strongest. This calculated judgement would significantly develop understanding surrounding the causes of Parkinson's disease and help researchers determine whether the gut microbiota is something they must therapeutically regulate and monitor in patients to reduce the disease's onset, as well as the symptoms that accompany it.

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Role Of Gut Microbiota In Parkinson's Disease:

Aggregation Of Alpha Synuclein:

Alpha synuclein is a key protein involved in Parkinson's disease, with its aggregation affecting dopaminergic neurons in a multifactorial manner.[11] When in a state of dysbiosis, the intestinal lining can become disrupted, allowing for the movement of endotoxins into the bloodstream.[12] These toxic components on the outer membrane of numerous gut bacteria can interact with receptors on immune cells and trigger a strong, systemic inflammatory response affecting the brain.[13] As a result, intracellular chaperone proteins, particularly those located in the cytoplasm and associated with organelles like the endoplasmic reticulum and lysosomes, can become downregulated in neurons and ineffectual when it comes to binding or protecting client proteins. As a result, cellular protein homeostasis cannot be maintained, leading to the misfolding and aggregation of alpha synuclein into Lewy bodies.[14]

These bodies are prone to disrupting the proteasome, which degrades ubiquitinated proteins, and autophagy, a process where dysfunctional proteins are engulfed, in the protein quality control systems of dopaminergic neurons.[15,16] Consequently, a proteotoxic environment is created within, inducing irreversible damage to the cell.[17] This can significantly affect dopamine production and its release, as neurons cannot function naturally. Moreover, Ruz *et al*. state that stress formation on the endoplasmic reticulum (ER), mitochondrial dysfunction, and defective neurotransmission (which, if prolonged, could lead to neuronal death) are all also exacerbated and further increase the risk of Parkinson's disease.[18]

Alpha synuclein aggregates are also amphipathic, which makes it easy for them to accumulate in the inner mitochondrial membrane found inside dopaminergic neurons. Here, they are known to inhibit complex 1 of the electron transport chain, NADH dehydrogenase, causing a reduction in ATP production for the cell as a whole.[19] This is detrimental for dopaminergic neurons as they require lots of energy to establish ion gradients for dopamine shuttling into vesicles.[20] Not having sufficient levels to do so exacerbates the risk of cellular energy failure and depletions in dopamine release, both of which negatively impact behavioral and motor control.

Moreover, harmful changes in the gut microbiome composition can activate the vagus nerve, which transmits inflammatory signals to the brain,[21] an environment that can strongly influence the aggregation of alpha synuclein.[22] Post-aggregation, the interactions these proteins have with ATP synthase can open the mitochondrial permeability transition pore, resulting in mitochondrial swelling due to the influx of ions and water.[23] This can rupture the outer mitochondrial membrane, releasing pro-apoptotic factors into the cytosol, ultimately evoking programmed neuronal cell death.[24] As a result, the basal ganglia circuits can be impaired.

Contrary to their normal role in the presynaptic terminals, aggregated alpha-synuclein, instigated by bacterial changes, can also interfere with synaptic function in dopaminergic neurons.[25] This is because aggregated Alpha synuclein impedes vesicle recycling- the process where synaptic vesicles are reloaded with neurotransmitters and returned to the synaptic terminal. This does not allow for effective exocytosis of synaptic vesicles containing neurotransmitters, making neurons unable to communicate with one another effectively.[26] Communication is worsened by alpha synuclein's disruption of calcium homeostasis, increasing intracellular calcium concentration.[27] Consequently, Calpains are activated, which are intracellular proteases that have been shown in studies to break down axonal integrity, leading to further stunting in electrical signal transmission between neurons, causing them to dysfunction.[28]

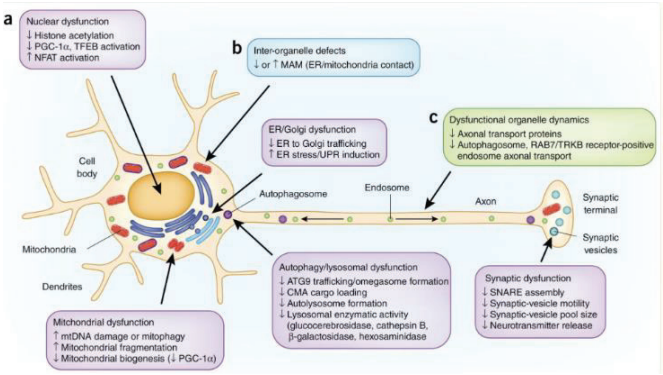

Figure 1: Summation of the different pathways in which alpha synuclein causes toxicity to a neuronal cell from Wong *et al*.[29]

Additionally, small oligomers, clusters of alpha synuclein toxic to cells, adopt a prion-like behavior where they can self-propagate.[30] This occurs by promoting normal alpha synuclein misfolding in a neighboring neuron, leading to the progressive accumulation of toxic aggregates in different brain regions. This has been proven through an observation of α-synuclein aggregation in grafted fetal mesencephalic progenitor neurons several years after transplantation,[31] leading to neurodegeneration, which continues to be a main contributor to Parkinson's disease. Therefore, the aggregation of alpha synuclein into Lewy bodies because of leaky gut, and the bidirectional communication between the gut and brain through the vagus nerve, causes a variety of issues that significantly affect the functionality of dopaminergic neurons, causing Parkinson's disease.

Increased Permeability of Blood to the Brain Barrier by Inflammatory Cytokines:

Gut dysbiosis triggers an innate immune response, which leads to the excessive secretion of pro-inflammatory cytokines.[32] These proteins enhance the permeability of the blood-brain barrier (BBB) to toxic substances, significantly influencing the development of Parkinson's disease. The BBB is a structure that plays a crucial role in protecting the brain from unwanted molecules circulating in the blood by exerting a strong diffusional restriction on exchange.[33] However, excessive amounts of pro-inflammatory cytokines can reduce the structural integrity of this endothelial cell barrier by altering the tight junction (TJ)-associated proteins such as claudins, occludin, and junction adhesion molecules. These proteins are essential for maintaining the barrier's tightness and preventing "leakage."[34]

Tumor necrosis factor (TNF-α) and interferon-gamma (IFN-γ) are particularly disruptive to TJs as they bind to endothelial receptors and activate signaling pathways that increase myosin activity, a motor protein that moves along the cytoskeleton and aids cell contraction. This leads to the abbreviation and remodeling of the endothelial cytoskeleton, creating gaps between cells and disrupting TJs, ultimately allowing larger solutes to pass through to the brain. This separation also causes TJ protein mislocalization, from their original position in the plasma membrane, to the cytoplasm, which compromises their function.[35] These issues increase Parkinson's disease onset, as they make it easier for harmful substances and cells to enter the brain. For example, pathogens can enter and activate immune cells, leading to the release of inflammatory cytokines, damaging dopamine-producing neurons in the substantia nigra.[36]

Interestingly, interleukin-22 and 6, as mentioned by Takuya Suzuki *et al*., can increase the production of claudin-2 tight junction proteins in endothelial cells.[37] However, claudin's role of increasing sodium and water passage through paracellular channels lowers resistance to these ions moving in between cells and therefore increases their rate of movement through the BBB.[38] This disruption of ion homeostasis can contribute to the onset of Parkinson's disease, as the brain is highly sensitive to changes in ion flux.[39] Additionally, the accumulation of ions in the brain's extracellular space can affect synaptic signaling and lead to cerebral edema through osmosis.[40] This can cause neurological impairment and reduced signal transmission between neurons, eventually resulting in a decrease in dopamine transport. Consequently, individuals affected exhibit symptoms such as uncontrolled shaking and instability.[41]

Moreover, higher levels of ions can lead to excitotoxicity, where neurons transmit incorrect signals at an excessive rate as they activate ion channels that are sensitive to aberrant amounts. This can result in a loss of function or apoptosis of these overexcited cells,[42] the main mechanism of neuronal loss in Parkinson's disease.[43]

So, the release of proinflammatory cytokines, because of gut dysbiosis, plays a significant part in neurodegeneration by increasing BBB permeability. This allows for harmful substances to seep through the membrane, exacerbating damage and death of dopaminergic neurons. The lack of the neurotransmitter dopamine, in particular, means the brain loses a crucial neuroprotective factor, inevitably exacerbating the onset of Parkinson's.[44]

Overactivation Of Microglia by Proinflammatory Cytokines:

When high levels of proinflammatory cytokines are released by the immune system due to the translocation of toxins and immune substances across an imbalanced gut's 'leaky' barrier,[45] the vagus nerves' sensory fibers can be activated.[46] This acts as a communication link between the gut and brain, allowing cytokine signals to overactivate microglial cells. As a result, microglia change shape and secrete reactive oxygen and nitrogen species as part of their immune response, influencing oxidative stress. This process occurs in the presence of excessive free radicals and inadequate levels of antioxidants to get rid of them, aggravating Parkinson's disease in a multifactorial manner by affecting both neurons and synapses.[47]

Specifically, reactive oxygen species can attack the cell membranes of neuronal cells in a process called lipid peroxidation due to their composition being a phospholipid bilayer.[48] This disrupts the membrane's integrity and results in substances moving into the cell that would originally be too big or charged to enter, leading to the cell losing functionality.[49] Although lipid peroxidation directly affects the cell membrane, its byproducts, formed from attacking polyunsaturated fatty acids, such as 4-hydroxynonenal, can also be toxic for highly sensitive dopaminergic neurons.[50]

Coincidentally, dopamine oxidizes readily with reactive oxygen species to form dopamine quinones. These are chemically reactive molecules that break DNA and covalently bond to amino acid residues in proteins, affecting their function and structure. This process significantly damages dopaminergic neurons, as a single neuron contains about 50 billion proteins essential for its functions.[51] The loss of these neurons significantly worsens Parkinson's severity by creating an imbalance between excitatory and inhibitory signaling in the basal ganglia, which they previously kept stable.

A main consequence of this imbalance is increased glutamate release, a neurotransmitter that produces action potential signals that rapidly change in voltage, further contributing to excitotoxicity and neuronal death.[52] Furthermore, excitotoxicity also impairs mitochondrial function by inducing DNA damage and endoplasmic reticulum stress. This reduces ATP production, which is a molecule essential for providing energy through phosphorylation. As a result, the high energy demands of dopaminergic neurons cannot be met, leading to a decline in their function, meaning motor control worsens in Parkinson's patients. Moreover, this induces mitochondrial membrane permeabilization to release proapoptotic factors from the intermembrane space, leading to neuronal death.[53]

Withal, evidence indicates that triggered microglia, as a consequence of gut dysbiosis, create a cytokine-rich environment that can activate intracellular signaling pathways, primarily the nuclear factor kappa light chain enhancer of activated B cells (NF-kB), due to the blood-brain barrier (BBB) being lined with TNF and IL-1 receptors.[54] This process can upregulate the expression of adhesion molecules such as integrins and selectins on endothelial cell surfaces, which can amplify Parkinson's disease as they allow for the trans endothelial migration of immune cells through the barrier.[55] This creates a cycle of continuous activation of microglia and peripheral immune cells, leading to chronic neuroinflammation.[56] Not only does neuroinflammation impair neuronal repair mechanisms, resulting in a permanent reduction in dopamine levels, but it also diminishes synaptic functions by inducing dopamine-related neuronal injury in the basal ganglia.[57]

Synaptic plasticity, in particular, the ability for synapses to weaken or strengthen in response to activity, is notably dysfunctional due to neuroinflammation. This leads to disrupted cognitive function and reduced dopamine-related neuronal efficiency, ultimately creating a lack of communication between brain regions.[58] Therefore, the overstimulation of microglial

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cells in the brain, deviating from their rest state, makes them particularly toxic for the brain and leads to numerous issues regarding neurons, their organelles, and brain junctions, which aid Parkinson's hallmark symptoms of motor issues, incoordination, and cognitive impairment.

Short Chain Fatty Acid Reduction Inducing Neuroinflammation:

Another major consequence of gut dysbiosis is a reduction in vital microbial diversity.[59] This means that the gut contains a smaller pool of beneficial species, such as *Firmicutes*, which have been shown by studies to break down complex polysaccharides through hydrolysis to produce butyrate and other short-chain fatty acids (SCFAs).[60] Once produced in the gut, butyrate can be absorbed into the bloodstream and pass through the BBB to reach microglial cells. These cells have G-protein-coupled receptors on their cell membranes, which, when activated by butyrate, allow microglia to shift from their pro-inflammatory phenotype to an anti-inflammatory one, reducing the risk of chronic neuroinflammation.[61]

A depletion in SCFAs, however, limits this process and can create an inflammatory environment, impairing microglia, which play a significant role in clearing amyloid beta peptides through phagocytosis.[62] While these peptides are formed frequently through normal cellular processes, microglia dysfunction means they can accumulate and form plaques that are toxic to surrounding dopaminergic neurons,[63] leading to impaired function and eventual cell death. This damage and buildup can contribute to the development of Parkinson's disease and dementia that comes with it, characterized by a progressive deterioration in both memory and attention.[64]

Prolonged Inflammation, originating from dysbiosis-induced SCFA reduction, can also increase levels of certain inhibitory neurotransmitters, such as Gamma-aminobutyric acid (GABA) in the brain.[65] These block nerve signal transmission in the brain, suppressing the activity of dopaminergic neurons, which rely on regular communication to stay stimulated.[66] If this process continues persistently and at a high level, as a result of chronic inflammation by SCFA depletion, neurons necessary for dopamine release can shrink and lose connections.[67] Consequently, the dopaminergic neurons degenerate, which is a prevalent issue relating to Parkinson's development, and depending on the area in which this happens, can even evoke emotional imbalances or motor circuit suppression.[68]

SCFAs are also importantly linked to the promotion of brain-derived neurotrophic factor production (BDNF).[69] These promote neuronal health in a multifactorial manner, one of which is through the stimulation of new neuronal growth, which is important for brain repair after injury or neuroinflammation. It also allows for the replacement of dopaminergic neurons, which may have undergone apoptosis, inhibiting the onset of Parkinson's.[70] SCFA reduction, however, because of its diminished synthesis by gut bacteria, means there is a significant loss of these beneficial neurons and a significant decline in axonal growth, which BDNFs are known to promote. This means neurons cannot efficiently receive signals and establish new connections for communication, enhancing the likelihood of Parkinson's disease, which is characterized by the loss of these nerve cells.

Lastly, SCFAs play an important role in the function and differentiation of regulatory T cells, which maintain immune homeostasis by suppressing excessive immune responses.[71] The absence of fatty acids, though, means that chronic neuroinflammation can occur, exacerbating excessive cytokine release and the creation of a vicious cycle of neuronal loss.[72] So, Gut dysbiosis causes a profound reduction in SCFA-producing bacteria, which leads to neuroinflammation, enhancing Parkinson's disease through its adverse effects on dopaminergic neurons.

Digestion Of Tyrosine Attributed to Bacterial Overgrowth:

The reduction of dopamine, a key factor influencing the severity and onset of Parkinson's disease, can also be exacerbated by the over-representation of certain bacterial species in a gut microbiome that comes with dysbiosis, resulting from changes in both lifestyle and bodily environments. Research indicates that high-protein diets, for instance, can promote the growth of *Clostridium* species, while *Lactobacillus* thrives in more acidic conditions.[73] Both of these bacterial types, along with many others, metabolize tyrosine, which is an aromatic amino acid that plays a crucial role in the production of neurotransmitters such as dopamine. This process occurs through the conversion of tyrosine to levodopa by the enzyme tyrosine hydroxylase, which is subsequently transformed into dopamine.[74]

Specific pathways in which tyrosine is utilized by bacterial species include tyrosine decarboxylation, where it is turned into tyramine, and fermentation, where it becomes organic acids, alcohols, or gases to generate NADH.[75] As a result of this excessive usage of tyrosine, the brain cannot synthesize enough dopamine to sustain adequate levels in dopaminergic neurons situated in the substantia nigra. This can result in rigidity, bradykinesia, and enhance the emotional changes associated with Parkinson's disease.

Moreover, tyrosine produced in the gut has neuroprotective roles in the form of oxidative stress reduction through its antioxidant properties.[76] This can be attributed to its aromatic ring structure, which allows it to donate electrons to stabilize ROS and free radicals. Therefore, a decrease in this amino acid can lead to neurodegeneration and neuronal cell death through a combination of apoptotic signaling pathways activated by ROS, excitotoxicity, and biological molecule modification.[77] So, changes to internal gut conditions can lead to the proliferation of certain bacteria, resulting in a state of dysbiosis. This bacterial buildup can contribute to the development of Parkinson's disease by utilizing excessive tyrosine, leaving an insufficient amount for dopamine production and the maintenance of neuronal health.[78]

Diet	Bacteria Altered	Effect on Bacteria
High-fat	*Bifidobacteria spp.*	Decreased (absent)
High-fat and high-sugar	*Clostridium innocuum, Catenibacterium mitsuokai, Enterococcus spp.*	Increased
Carbohydrate-reduced	*Bacteroides spp.*	Decreased
	Bacteroidetes	Increased
Calorie-restricted	*Clostridium coccoides, Lactobacillus spp., Bifidobacteria spp.*	Decreased (growth prevented)
Complex carbohydrates	*Mycobacterium avium subsp. paratuberculosis, Enterobacteriaceae*	Decreased
	B. longum subsp. longum, B. breve, B. thetaiotaomicron	Increased
Refined sugars	*C. difficile, C. perfringens*	Increased
Vegetarian	*Escherichia coli*	Decreased
High n-6 PUFA from safflower oil	*Bacteroidetes*	Decreased
	Firmicutes, Actinobacteria, Proteobacteria	Increased
Animal milk fat	*δ-Proteobacteria*	Increased

Figure 2: This table shows that different dietary patterns significantly alter gut microbiota composition. High-fat, high-sugar, and animal-based diets promote bacteria associated with dysbiosis, while plant-based or complex-carbohydrate-rich diets tend to support more beneficial bacterial populations.[79]

Gut Dysbiosis As A Secondary Effect Of Parkinson's Disease: Reduced Gut Motility in Parkinson's:

Many studies carried out in the last eight years by researchers in the field of gut dysbiosis have suggested that the change in bacterial composition is a result of Parkinson's disease, rather than a cause. This is because the disease can deplete dopaminergic neuron quantities in the enteric nervous system, ultimately slowing down the passage of food through the digestive tract, a process called gastric emptying.[80] The reason for this is a loss of dopamine, which causes rigidity and tremors of smooth muscle, typically necessary for efficient and coordinated contractions in peristalsis.[81] As a result, food waste stagnates in the gut for long periods of time, creating a favorable environment for pathogenic bacteria to proliferate.[82] This can exacerbate a variety of problems, one of which is the increased competition due to new bacteria entering the microbiome, leaving fewer nutrients and resources for all species to survive[83] Moreover, the alteration of PH levels, by certain harmful bacteria, through the formation of acidic metabolites can also evoke dysbiosis by reducing less PH resistant populations like *Bifidobacteria* and *Lactobacilli*.[84]

In addition to sluggish gastric emptying, chronic constipation is one of the most common digestive problems in Parkinson's disease, occurring in over 50% of patients.[85] This is where egestion becomes difficult because of delayed colonic transit time, and is caused by Parkinson's disease affecting the parasympathetic system, which stimulates digestion and motility.[86] Prolonged durations in this state, however, can increase the likelihood of excessive fermentation, as bacteria have more time to metabolize undigested food particles. Not only does this facilitate bacterial growth, but it also leads to toxin production in some cases.[87] This can create an inflammatory environment that exacerbates intestinal permeability and damages the intestinal mucosa,[88] a moist inner lining of the gut that protects the bacteria from invasive pathogens and abrasive particles, further limiting growth.[89]

Parkinson's disease affects the smooth muscle, which decreases bile flow from the gallbladder into the intestines due to its widely researched influence on duct functionality.[90] Bile is important for the emulsification of lipids, and reduced concentrations can lead to the malabsorption of fats. This means that these molecules will remain in the intestine for longer, serving as a food source for certain types of bacteria. Once these foods are used, byproducts such as long-chain fatty acids and lipid metabolites can form,[91] which are associated with dysbiosis and impairment of intestinal barrier function as mentioned by Joe *et al*.[92]

On top of this, bile is interestingly involved in signaling, where it interacts with nuclear receptors such as pregnane X (PXR). This receptor stimulates the reduction of intestinal inflammation, meaning less bile exacerbates swelling.[93] Consequently, the gut's oxygen levels increase, which contrasts with the anaerobic environment typically found in the intestines.[94] This creates conditions more favorable for facultative anaerobic pathogens like *Enterococcus*, further promoting dysbiosis.[95] Chronic inflammation, creating unfavorable environments, also makes the formation of pathogenic biofilms more likely. These are clusters of bacteria that stick to surfaces in the gut and are protected by a self-produced slimy matrix.

As a result, pathogens become more resistant to immune responses, making it harder for the body to clear them out, leading to the persistence of harmful bacteria in the microbiome.[96] So, Parkinson's disease's effects on dopaminergic neurons and the parasympathetic system can lead to severe bile flow dysfunction and a decline in gut motility. All these contribute towards altering the variety of bacteria in the gut microbiome.

Effects Of Parkinson's Influenced Sleep Deprivation on Gut Dysbiosis:

Sleep disturbances are often exhibited by Parkinson's disease patients, 80% of whom suffer from fragmented rest.[97] This is due to symptoms such as insomnia, restless leg syndrome, and stiffness, which all play a part in creating an extremely uncomfortable environment. These issues usually precede motor symptoms and impair the circadian rhythm of the body, which is a 24-hour internal clock that regulates sleep-wake cycles and hormone release, leading to disrupted populations of gut bacteria.[98] This is because disturbances to the internal clock can cause misalignments between gut microbial timings and the body's consistent rhythms of digestion, activation, and rest. The gut microbiome thrives on this predictable schedule, with 10-15% of species' abundances being determined by time of day.[99] So, when the times are altered because of irregular sleep patterns, imbalances in populations occur. This could facilitate the excessive buildup of pathogenic species and the inhibition of useful ones, which could be harmful to the microbiome.[100]

In addition to this, altered sleep patterns can also affect hormone secretion. Cortisol, in particular, is released in a rhythmic pattern, peaking in the morning and gradually decreasing throughout the day. Waking up and sleeping inconsistently, however, often results in persistent higher levels of cortisol at night, which can inhibit the production of estrogen.[101] The re-

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dundancy of this hormone can reduce the growth of beneficial bacteria involved in the fermentation of dietary fibers, leading to an underexpression of these species.[102] Excessive levels of cortisol can also evoke inflammation, which limits the growth of numerous populations.[103]

Melatonin, another hormone influenced by sleep deprivation, typically increases in the evening as part of the body's natural sleep-wake cycle.[104] However, irregular sleep patterns caused by Parkinson's can disrupt this cycle and cause melatonin to rise at a later time. This can lead to waking up at night and a lack of restful sleep, which plays a further part in lowering the overall production of this hormone.[105]

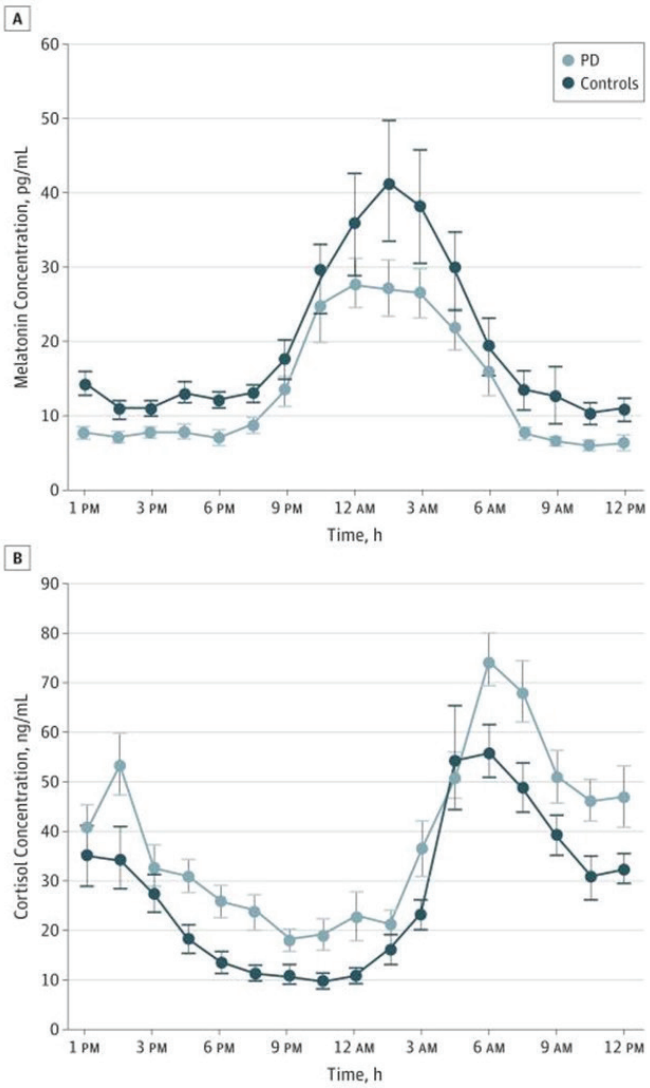

Figure 3: Two graphs comparing the mean (SEM) serum melatonin and cortisol concentrations at each time point between Parkinson's disease and healthy individuals. These show that individuals with the disease have a blunted circadian rhythm of melatonin secretion with lower nighttime peaks compared to controls, suggesting impaired sleep-wake regulation. Additionally, Parkinson's patients show a dysregulated cortisol rhythm with higher daytime and early morning cortisol levels than controls.[106]

While melatonin is primarily known for its role in regulating the sleep-wake cycle, its release into the circulatory system by the pineal gland also has other important functions, such as acting as an anti-proliferative, antiangiogenic, and antioxidant hormone.[107] Studies have shown that melatonin can inhibit the growth of harmful microorganisms by interfering with their DNA replication while undergoing binary fission. This is achieved through regulating the expression of genes associated with cell division, which prevents pathogenic bacteria from replicating and forming identical daughter cells.[108]

Therefore, a decrease in melatonin production can significantly enhance the growth of pathogenic bacteria, leading to dysbiosis. Additionally, a reduction in melatonin levels due to changes in sleep patterns can increase the levels of ROS and NOS in the gut.[109] This has been demonstrated in studies on mice intestinal microbiota, where melatonin was found to regenerate other antioxidants such as vitamin C and E, allowing them to continue protecting gut bacteria by limiting damage to their DNA, proteins, and lipids.[110]

Melatonin has also been proven by research to play a role in reshaping the gut microbiota and alleviating inflammation through the modulation of immune cell activation.[111] So, a reduction in this hormone ultimately contributes to a decrease in microbial diversity and levels of beneficial bacteria, leading to dysbiosis. In conclusion, sleep deprivation, a common symptom among Parkinson's disease patients, significantly contributes to the development of gut dysbiosis through changes in hormone levels and a dysfunctional circadian rhythm.

Discussion

This literature review discusses the ongoing debate surrounding whether gut dysbiosis is a secondary effect of Parkinson's disease, exacerbated by the numerous motor and systemic changes it evokes, or a direct cause of the disease.

One challenge in conducting this review was the inconsistency in sample sizes among existing studies, which can introduce variability as well as make it difficult to compare data and determine its reliability. While some studies, such as a genome-wide association study by Chang *et al.*, which identifies 17 new Parkinson's disease risk loci from 6400 cases and 300,000 controls, use large sample sizes to conduct and analyze genetic variants associated with the disease,[112] others have only included around 20 controls, making them insufficient.[113] As a result, a selective approach was taken in deciding which research to include in this paper, ensuring that all relevant points were supported by tangible evidence. Priority was given to peer-reviewed articles that represented thorough experimental designs, such as longitudinal cohort studies and clinical trials.[114]

This comprehensive approach to data extraction, combined with a focus on recent studies (primarily post-2014), has allowed for a more nuanced understanding of the impact of the microbiota on Parkinson's disease and the disease's effect on dysbiosis. By focusing on modern papers, outdated and potentially incorrect information has also been avoided. However, it was challenging to find many recent papers when researching tyrosine and its neuroprotective roles, with the majority published between 1995 and 2014.

Some methods, such as collecting fecal samples from Parkinson's patients, as seen in a study by Ilhan *et al.*,[115] can be logistically challenging. Variables, including keeping the sam-

ple fresh to limit bacterial growth, must be carefully controlled to avoid introducing biases in sample collection and analysis. This issue is highlighted in a scoping review by Khan *et al.*, which also advocates for the use of more precise diagnostic devices for Parkinson's disease.[116] Therefore, this paper may include viewpoints that differ slightly from other gut microbial researchers due to the varying reliability of certain methodologies. However, in the selective process, experiments with numerous variables have been avoided as much as possible.

Through this review, it has become clear that the most prevalent mode of action is the influence of gut dysbiosis on Parkinson's disease. Specifically, its impact on aggregating alpha-synuclein, dysregulating immune responses, and reducing short-chain fatty acid production has been found to be most significant in the onset of dopaminergic loss, which comes with this disease. This conclusion is supported by numerous meta-analyses, such as the one by Hiroshi Nishiwaki *et al.*, which conducted gene sequencing in 223 patients with Parkinson's disease, as well as many systematic reviews outlining the mechanisms behind the neurodegeneration, a hallmark of the disease.[117]

In contrast, the idea that Parkinson's disease leads to dysbiosis has less research and lower quality of evidence. While there are some outliers, such as a sophisticated meta-analysis by Romano *et al.*, which thoroughly examined the effects of intestinal inflammation on the microbiome, much of the evidence is limited to studies in mice, which may not necessarily translate to humans.[118] Therefore, it cannot be assumed that the findings in animal studies will have the same outcomes in a clinical setting.

While this is the overarching judgement, looking into this question of whether gut dysbiosis is a cause or effect of Parkinson's disease has also led to a new perspective. The relationship between Parkinson's and the gut may be bidirectional, where the gut bacteria affect and are being affected by the disease simultaneously. This dynamic interplay highlights the importance of considering both the gut and the brain in understanding the pathogenesis of Parkinson's disease, as both worsen concurrently. While some research, such as a study by Santos *et al.*, has focused on this aspect, further studies are necessary to fully understand this complex relationship and develop novel therapeutic interventions for managing the disease as a whole.[119]

■ Conclusion

Gut dysbiosis has long been recognized as a significant contributor to the development of Parkinson's disease through the range of issues it creates. The first half of this paper examines the primary effects of a dysregulated microbiota before delving into the secondary effects that these cause, such as the misfolding of alpha synuclein and increased BBB permeability, which are still being studied and proven by Parkinson's disease and gut microbiota researchers to this day.

The paper also considers the opposing argument, where gut dysbiosis is viewed as a consequence of Parkinson's induced lifestyle changes, such as sleep disturbances and reduced gut motility. Nevertheless, after analyzing the current body of research, which has represented both views, this literature review has predominantly pointed to gut dysbiosis as a significant initiator of Parkinson's disease pathogenesis rather than an effect.

Although this seems to be the case, a rigorous, multi-faceted research approach is still essential to better elucidate the causal or consequential nature of gut dysbiosis in Parkinson's disease and therefore strengthen this conclusion. One potential methodology involves longitudinal cohort studies, wherein individuals at risk for the disease are monitored over extended periods. By regularly analyzing their gut microbiota composition through stool samples and correlating these findings, using statistical tests, with the onset and progression of Parkinson's symptoms, researchers can determine whether dysbiosis precedes or follows disease manifestation. Including control groups of healthy individuals and patients with other neurodegenerative diseases would also strengthen the experiment's validity further. Similar tests are already being performed, such as a two-year follow-up study, which demonstrated that lower baseline levels of beneficial bacteria like *Bifidobacteria* were associated with worsening symptoms, suggesting a potential predictive role of gut microbiota in disease progression.[120]

Investigations into the temporal relationship between Parkinson's disease onset and gut microbiota changes must also become more frequent, thoroughly exploring prodromal stages of the disease. From similar research conducted so far, individuals with REM sleep behavior disorder (RBD), a precursor to the disease, exhibit gut microbiota alterations similar to those observed in Parkinson's patients.[121] This finding suggests that dysbiosis may precede motor symptoms, although it remains unclear whether it is a cause or an early effect of neurodegeneration, which must be resolved with more trials. Experiments in which germ-free mice are colonized with gut microbiota from Parkinson's disease patients could accompany this well, helping to determine whether gut microbiota alterations develop before or after neurodegeneration. A 2016 seminal study by Sampson *et al.* utilizes this methodology, finding numerous motor deficits and neuroinflammation present in modified mice.[122] This technique also allows for controlled manipulation of variables, being able to provide insights into the various underlying mechanisms between Parkinson's and gut dysbiosis stated in this literature review.

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I attest that the ideas, graphics, and writing in this paper are entirely my own. HS

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