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Review Article

Modulation of Parkinson's Disease by the Gut Microbiota

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Abstract

The gut microbiota consists of thousands of microbial species sharing a symbiotic relationship with the human host. These microorganisms have a well-defined role in maintaining optimal function through various avenues including metabolism and immunomodulation. A literature search was accomplished using Google Scholar, MEDLINE, PubMed, and relevant articles were nonsystematically reviewed. In states of dysregulation termed dysbiosis, the gut microbiota may play a role and can lead to various pathologies. Interestingly, pathological states are not entirely limited to the gut and have the potential to affect other systems. Notably, dysbiosis has been linked to several neurological pathologies, including Parkinson's disease (PD). Hallmarks of Parkinson's include buildup of Lewy bodies mediated by α-synucleinopathies, aggregation of misfolded proteins, and mitochondrial dysfunction, resulting in various motor and gastrointestinal dysfunctions. The gut microbiota is implicated in contributing to this pathology through communication via the gut–brain axis. While there have been preliminary findings indicating the potential for a causal role of the gut microbiota in PD, further research is required before making solid conclusions.

Keywords: Dysbiosis, gut microbiota, Parkinson's disease

Introduction

Gut microbiota refers to the community of microorganisms found within the gut, composed of a variety of bacteria, fungi, and viruses. Many of the bacteria found in this broad mix serve integral roles in maintaining homeostasis and immune and physiological functions. The community is thought to consist of 100 trillion archaeal and bacterial cells over 1000 species, with the majority belonging to the Firmicutes and Bacteroidetes families. These microorganisms help the host in various functions including nutrient metabolism, drug metabolism, and immunomodulation. These microorganisms can be regulated and promoted toward effective functioning by altering diet and uptake of substances known as prebiotics. However, if the normal microbiota composition becomes imbalanced, they go into a state termed dysbiosis. This altered, negative state can exacerbate and be the source of various pathologies. Many of these pathologies are naturally related to the gastrointestinal (GI) tract (i.e., inflammatory bowel disease [IBD]); however, they can affect other systems as well, including the neurological system.[1-5] Thus, this article aims to first review the normal function of the gut microbiota and its relationship with the neural system and then examines the hallmarks of Parkinson's disease (PD) and the potential role of the gut microbiota in PD.

Methods

This is a nonsystematic review exploring the role of gut microbiota dysbiosis in PD. A search of the literature was done using online databases (PubMed, Google Scholar, and MEDLINE) with the following search terms in various combinations: Gut Microbiota, Dysbiosis, Parkinson's, Parkinson's Disease, Gut Microbiota-Brain Axis, Gut-Brain Axis, Neurodegenerative. Relevant records were retrieved and reviewed.

The article aimed to determine the current state of the literature regarding the role of dysbiosis on PD and any pathways which may have been implicated in the pathogenesis. Additionally,

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relevant information on PD pathogenesis in general was acquired to have a thorough understanding. The initial draft was by the authors via several rounds of multilateral electronic communications. All authors approved the final version.

Gut Microbiota: Normal Function

To appreciate the possible role of the gut microbiota in PD and its impact through the gut microbiota–brain axis, understanding of the normal function is required. This involves examining the role of the gut microbiota on nutrient metabolism, drug metabolism, and the interaction with the neural and endocrine systems.

Nutrient metabolism

The gut microbiota has a complex bidirectional relationship with the host, wherein the microbiota is capable of exerting effects on the host and *vice versa*.[1] The breakdown of complex carbohydrates and plant polysaccharides is a situation which exemplifies this relationship. Innate human enzymes are not capable of degrading these complex structures (i.e., cellulose, xylans, and resistant starch); however the gut microbiota is capable of this breakdown. The fermentation of these products by gut microbiota leads to energy for the microbiota itself, as well as end products such as short-chain fatty acids (SCFAs) including acetate, propionate, and butyrate. SCFAs can then have a diverse set of functions which include inflammatory modulation, vasodilation, aiding in gut motility, acting as an energy source, as well as wound healing.[6] The importance of the gut microbiota in metabolism and energy harvest for the host is well characterized by experiments done in germ-free mice.[1] It has been found that germ-free mice have twice as much fecal and urinary excretion of calories as compared to control mice. To compensate for this significant loss, these mice require a highly increased food intake, contributing to obesity.[7] These same mechanisms – while not explored – can also be applied to humans, highlighting the importance of the community. Another example highlighting the gut microbiota's effect on host metabolism is the diversification of bile acids. Bile acids which are crucial to the metabolism of substances such as fats can be deconjugated and metabolized into secondary bile acids, thereby diversifying the portfolio of the host and aiding in metabolism.[8]

Interestingly, the diet of the host also has profound impact on the composition and, consequently, the function of the gut microbiota. The composition of the gut microbiota has been found to be highly connected to the diet of the host, and less so to the sex, age, and nationality of the host.[9] It is important to recognize that while all these factors most definitely play a role in composition, diet is most likely the predominant factor.[1] Different types of diets have been found to be associated with different gut microbiota compositions. It has been reported that diets rich in protein and animal fat are associated with gut microbiota dominated by *Bacteroides*, while diets rich in carbohydrates are associated with gut microbiota colonies rich with *Prevotella*.[10]

While these associations exist, they lie more so on a gradient than as clearly distinct enterotypes within the host.[1] Changes in composition generally reflect a long-term change in diet as opposed to single meals or a series of meals. For example, it has been shown in mice that a 10-day dietary intervention was not sufficient to exert an effect on the gut microbiota.[10]

Drug metabolism

In addition to nutrient metabolism, the role of the gut microbiota has also been highlighted in drug metabolism. Much like the other facets of the gut microbiota–host interactions, the variability of the microbiome leads to highly individualized responses in drug metabolism.[11] These effects are primarily exerted through the secretion of microbial drug-metabolizing enzymes as well as microbiota–host co-metabolism.[4] Drugs metabolized through microbiota-dependent mechanisms can result in active, inactive, or even toxic metabolites. This metabolism can then result in increasing or decreasing efficacy of various drugs, including those associated with heart disease, gastric ulcers, and PD.[12,13] The effect of the gut microbiota on drug mechanisms is an area that has very recently begun to be explored critically, and is something that needs to be factored into future drug development and treatment plans.

Immunomodulation

The gut microbiota once again possesses an interesting bidirectional relationship with the immune system, much like it possesses with host metabolism. Gut microbiota are thought to be relevant to both healthy and diseased immune states within the host, having the capability to exert both beneficial and damaging effects dependent on various factors.[5] Germ-free mouse models once again provide an informative model, providing information on the importance of the microbial community. Chiefly, germ-free mice have displayed irregularities in the development of gut-associated lymphoid tissues, antibodies, Peyer's patches, and mesenteric lymph nodes.[14] Furthermore, the intestinal epithelial cells – a vital cog of the innate immune system – can become altered with different patterns of the gut microbiota, having altered distributions of microvilli and pattern recognition receptors.[15] Moreover, the adaptive immune system is also profoundly affected, having been shown to have decreased T-cell trafficking, as well as decreased secretion of important cytokines (i.e., interleukin [IL]-25).[5] The combination of all these factors has been shown to cause germ-free mice to be significantly more susceptible to infection than their healthy counterparts.

Alternatively, the gut microbiota can have a positive impact upon the host, promoting useful immune function. Probiotics, a term given to microorganisms with a beneficial impact on the host, have been found to exert these positive effects through various methods, including via the immune system.[3] These beneficial bacteria have been shown to regulate Tregs, and consequently secretion of IL-10 and transforming growth factor (TGF)-B and immunoregulatory molecules that prevent damaging inflammation. The therapeutic potential of these

mechanisms has been displayed in colitic mice. Treatment of colitic mice with a probiotic cocktail of bacteria (VSL #3) caused an increase of IL-10 and TGF-B secretion. However, more interestingly, transfer of VSL #3 lamina propria mononuclear cells displayed a protective and preventative effect against colitis.[16] As another example of probiotic treatment, it was shown that in a model of pathogen-induced inflammation, treatment with Bifidobacteria infantis leads to decreased intestinal inflammation and increased Treg cells.[17] While these are examples in mouse models, probiotic treatment is also very promising in human models.

Prebiotics

Prebiotics denotes "the selective stimulation of growth and activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host."[3] The gut microbiota is constructed based on a variety of factors, including genetics, sex, age, immune system, and comorbidities. In many cases, a nonfavorable composition of gut microbiota can be formed, hindering proper functioning. Thus, the use of prebiotics is helpful in these cases to selectively increase beneficial activity of the gut microbiota. An example of this is the use of dietary fructans (i.e., inulin fructans) to selectively increase the activity of Bifidobacteria in the context of obesity.[18] These substances act as a substrate for Bifidobacteria, which can then express B-fructofuranosidase, leading to an increase of development and activity within the gut. This increase has been shown to be inversely correlated with the development of fat mass, glucose intolerance, and lipopolysaccharide (LPS) level, highlighting the positive effects.[18] Besides, overexpression of host genes associated with inflammation and adiposity was prevented following prebiotic administration. Obesity is just one example of the beneficial effects of prebiotic administration, as the increased beneficial effects could be applied to a wide range of gut microbiota-affiliated pathologies.[3]

Gut Microbiota–Brain Axis

A relatively new phenomenon that has been highlighted is the interaction between the gut, and specifically the microbial colonies, and the brain is termed the gut microbiota–brain axis (GMBA). Communications between the two groups can occur through several modalities, including the neural system (neuroanatomical pathway), neuroendocrine pathway, immune systems, and metabolic pathways.[19] These bidirectional communication paths can have several implications on the body system, either contributing to homeostasis, or leading to pathology in the case of dysregulation. The bidirectional effects have been studied through various models, including the classical germ-free mouse model and various disease models. This axis has been implicated in pathologies including autism spectrum disorder, Alzheimer's disease, and PD. The importance of the GMBA has also been displayed by the high comorbidities of irritable bowel syndrome (IBS)/inflammatory bowel disease (IBD) and several stress-related neural issues.[19]

Neuroanatomical pathways

The gut microbiota and the brain can interact directly through the nervous system, which is primarily mediated by the vagus nerve, enteric nervous system (ENS), and the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS). Based on this sectioning, the neuroanatomical section can be placed in a four-division hierarchical standing. These are (1) ENS (including the myenteric ganglia, submucous ganglion, and gut glial cells), (2) prevertebral ganglia which regulate peripheral visceral reflex responses, (3) ANS (including T5–L2 sympathetic division, and the S2–S4 parasympathetic division), and (4) higher brain centers (information from cortex and subcortical centers funneling down to brainstem nuclei and controlling various gut functions).[20] The most direct route of communication between the two systems lies within the vagus nerve, through bidirectional communication having anti-inflammatory capabilities within the gut.[21]

Neuroendocrine pathways

The gut microbiota can interact with the neuroendocrine pathways, primarily through the hypothalamic–pituitary–adrenal (HPA) axis to result in various systemic effects, primarily associated with stress.[19] Germ-free mice have displayed an increase in corticosterone and adrenocorticotropic hormone, both associated with the HPA. Levels of these hormones have been shown to partially return to normal levels through fecal microbial transplant. Additionally, the importance of a healthy microbial community has been clearly outlined concerning the development of a healthy stress response within postnatal development. Again, this was displayed in the comparison of stress responses between germ-free and regular mice. Furthermore, germ-free mice have shown altered expression of brain-derived neurotrophic factor, NMDA receptor, and 5-HT1A receptor, all of which are involved in the stress response.[22] Conversely, stress can also have an impact on the gut microbiota, potentially leading to dysfunction and eventually pathology. This has best been displayed in rat models undergoing maternal separation. Maternal separation has been shown to cause a long-term change in the HPA, and consequent long-term change to the gut microbiota. It was found these mice had decreased levels of regular bacterial species such as Bacteroides in the cecum, and an increase in Clostridium. This also leads to increased levels of stress-inducible bacteria such as *Enterococcus faecalis* and *Pseudobutyri vibrio*.[23]

Neurotransmitters

Gut microbiota can also communicate with the nervous system through the production of several neurotransmitters. The microbial community can result in the production of various substrates, including gamma amino acids, butyric acid, 5-HT, dopamine, and SCFAs. While all the neurotransmitters have a considerable impact on the nervous system, 5-HT has been shown to have the most profound effect concerning the brain. In addition to these neurotransmitters, bacterial enzymes and

reactions can lead to the production of various toxic products such as D-lactic acid and ammonia. However, the extent of the effect of these critical molecules on the human body has not yet been elucidated clearly.[19,24]

Effect on development

In addition to interacting with the nervous system to ensure normal functioning of the body, the gut microbiota is thought to have a role in the development of the brain, and specifically the blood–brain barrier. This has been shown in the context of stress-induced models of mice having an increase of LPS and cytokine production, leading to increased permeability of the blood–brain barrier. The increase in permeability can lead to several critical effects, especially during the developmental stages. Temporally, the development of the nervous system and synaptogenesis highly overlaps with the time of gut microbiota development, again highlighting the correlation between the development of the two systems.[25]

Regarding a developing fetus, the maternal gut microbiome has the potential to exert various effects on the development of the nervous system throughout several of the mechanisms outlined. While many details of the mechanisms remain unclear, there are several theories regarding the interaction of the maternal gut microbiome and the developing fetus' nervous systems. For example, states of maternal gut dysbiosis can lead to the aberrant production of immunological substrates and cytokines that have an impact on the developing nervous system through changes in vagal/sacral neural activation pathways.[26] Additionally, the maternal HPA is thought to have an impact on development through the crossing of cortisol through the placenta, affecting various genes critical for neurodevelopment. Finally, maternal dysbiosis may lead to altered levels of neurotransmitters such as serotonin, which is implicated in neural cell division, differentiation, and synaptogenesis.[27]

Parkinson's Disease

PD is the second most common age-related neurodegenerative disease, affecting a large portion of the population. This disease is characterized by neurodegeneration in the substantia nigra pars compacta (SNpc), which is chiefly involved in the nigrostriatal dopaminergic pathway. The disease is primarily characterized by "parkinsonism," which consists of resting tremor, rigidity, slowness/absence of voluntary movement, and postural instability among other symptoms. While most cases (~95%) are thought to be sporadic (no genetic linkage), the pathogenesis of these cases is thought to be similar to the remaining inherited cases.[28,29]

From a pathological standpoint, PD is primarily characterized by a loss of nigrostriatal dopaminergic neurons and the accumulation of Lewy bodies (LB), which are intraneuronal proteinaceous cytoplasmic inclusions, composed of several proteins such as parkin, ubiquitin, neurofilaments, and α-synuclein.[30] The neurons in question primarily project to the putamen (an area of the brain that is heavily involved in movement), and thus there is a significant depletion of dopamine (DA) in the putamen, contributing to the characteristic symptoms seen.[31] The pattern of neurodegeneration seen in PD is distinctly different from degeneration solely due to aging, signifying that the pathogenesis involves significantly more factors than age.[32] While dopaminergic neurons are the primary target, noradrenergic, serotonergic, and cholinergic neurons show degeneration and accumulation of LB as well, contributing to various comorbidities commonly seen with PD.[28]

The cause of PD is very multifaceted, thought to include genetic predispositions in addition to environmental factors. Concerning environmental toxins, anyone toxin having a full effect has not been elucidated, yet several compounds have shown to be correlated with PD incidence. Of these compounds, some include things such as MPTP, paraquat (found in herbicides), and rotenone (used in lakes). It is postulated that either chronic exposure or single exposure leading to a cascade of negative effects could lead to the pathology associated with PD.[28,29] Regardless of the initial cause which provokes the pathways involved in PD, there are several systems which heavily contribute to the pathology seen in patients. Two primary systems include the aggregation and misfolding of proteins, in addition to mitochondrial dysfunction and consequent production of toxic reactive oxygen species (ROS) leading to deleterious effects.[28,29] These mechanisms are not mutually exclusive, though the exact connection between the two methods is yet to be elucidated. An example of their interaction includes oxidative damage leading to the misfolding of α-synuclein, contributing to LB and neurodegeneration.[33]

Misfolding and aggregation of proteins

Aggregation of misfolded proteins is a common feature of many neurodegenerative diseases, and PD is no different.[28] Misfolded proteins can exert their effect through a variety of pathways. For instance, they can directly cause damage through deformation of the cell, or interference of intracellular trafficking in involved regions. Furthermore, aggregations of misfolded proteins may cause sequestration of productive proteins. However, it is unclear if this method has a direct impact on PD pathogenesis.[34] Under normal conditions, the body has mechanisms by which it can clear the toxic protein aggregates, but in PD, these mechanisms are disrupted. Chaperone proteins and proteasomal degradation pathways both become involved in this pathogenetic pathway through a positive feedback loop which they lead to cellular dysfunction, which then further impairs the ability of these systems to prevent dysfunction.[28]

Mitochondrial dysfunction and oxidative stress

One leading theory in the role of mitochondrial dysfunction in PD involves the inhibition or other abnormalities in complex I of the electron transport chain. This theory was first discovered in MPTP models which showed irregularities along the chain.[35] This inactivity is not limited to the brain within the affected regions but can have systemic effects (i.e., irregularities found

in complex I of platelets).[36] This effect is thought to be due to a deficit inherited in the mitochondrial DNA, or a mutation in mitochondrial DNA from systemic toxicity, though no specific deficit has yet been discovered. The abnormalities in complex I lead to the production of ROS (i.e., superoxide, hydroxyl radical, and reactive nitrogen species such as peroxynitrite), which can then have deleterious effects through interactions with nucleic acids, proteins, and lipids.

These effects are once again involved in a positive feedback loop, wherein damage leads to the increased production of ROS, leading to further damage.[28]

Gene Models

While only a small proportion of PD cases are genetic, these pathways are essential to study as these cases still have a similar phenotype compared to the sporadic cases and may have similar affected structures/pathways. The main genes attributed to a role in PD are α-synuclein, parkin, ubiquitin C-terminal hydrolase L1(UCH-L1), and DJ-1. These genes are involved in both inherited cases and sporadic mutations.[28,29]

Synuclein

Dysfunction regarding synuclein in the context of PD is usually caused by separate missense mutations. Nevertheless, these mutations have not been elucidated in sporadic PD.[37] Regardless, they are still involved in some manner as shown by α-synuclein being a significant component of LBs.[30] Under normal conditions, α-synuclein is implicated in the proper functioning of synaptic vesicles within the presynaptic nerve terminals.[38] While the exact role is yet to be specified, dysfunction of the protein leads to altered cycles of synaptic function and further downstream effectors.[30] Furthermore, it has been discovered that α-synuclein may be involved in membrane binding and related protein trafficking. In the case of PD mutations, altered α-synuclein may be implicated in altered patterns of the DA transporter, contributing to dopaminergic neuron cell death.[39] Nevertheless, α-synuclein is thought to exert most of its effects through the contribution to LB. It has been shown that α-synuclein forms amyloid fibrils and more importantly protofibrils (nonfibrillar oligomers), contributing to neurodegeneration. As the two common genetic mutations associated with synuclein cause the protein to be significantly more prone to forming protofibrils, this pathway is thought to have a significant effect on pathogenesis.[37]

Parkin

Parkin is generally associated with recessively inherited modes of PD, and mutations can often be seen in patients with onset before the age of 30.[40] From a pathological standpoint, parkin-associated PD is characterized by a loss of SNpc dopaminergic neurons, though LBs are not thought to be a major component.[40] Parkin is an E3 ubiquitin ligase and is involved in the ubiquitin–proteasome system, specifically within the role of identifying and targeting misfolded proteins. As such, a mutation leads to the inability to adequately prevent the aggregation of such proteins, subsequently contributing to PD development.[41] Synuclein is also thought to contribute to proteasome dysfunction, and thus dysfunctional parkin–synuclein interactions may also contribute a role. However the exact interaction is yet to be elucidated.[42]

Ubiquitin C-terminal hydrolase L1

UCH-L1 is thought to be a "susceptibility" gene for PD, as an association between PD and a mutation in the UCH-L1 gene has been highlighted.[43] Yet, from a pathological standpoint, a significant effect has not been seen. UCH-L1 plays a role in the recycling of ligated ubiquitin following the degradation of misfolded proteins by the proteasome.[44] While mutations in the gene have shown a decreased effect in recycling, in mouse models null for UCH-L1, no PD-related neurodegeneration was seen.[45] Some polymorphisms have been shown to be protective of PD, further complicating its potential role in pathogenesis.[46]

DJ-1

DJ-1 gene mutations have been found in various pedigrees with autosomal recessive PD, though the exact role of DJ-1 is not known. In the context of PD, the role of DJ-1 that may be most implicated in pathogenesis is reacting to ROS. Under normal conditions, DJ-1 is thought to have a role in providing an adequate response to ROS. However, dysregulation of these pathways could again lead to PD.[47]

Gut Microbiota and Parkinson's Disease

As previously discussed, PD is a highly multifactorial disease without a clear etiology.[29] What is very interesting is that the brain is not the only organ affected as shown by the remarkable GI comorbidities with PD. It is currently approximated that 80% of PD patients suffer from constipation, abnormal salivation, dysphagia, and other symptoms related to the GI tract.[48] These symptoms have been shown to be related to α-synuclein accumulation and neurodegeneration within the ENS, which is very similar to the neurodegeneration that occurs in the SNpc in the context of PD. However, what is even more interesting is the thought of a causal relationship between gut microbiota dysbiosis and PD. This connection has been examined, as in many cases, GI-related symptoms are discovered in the initial stages of PD, occasionally even before motor hallmarks appear.[49]

GI dysfunction in the context of PD can also be multifactorial, as while some symptoms can be attributed to being secondary to dopaminergic deficiency due to nigrostriatal damage, other systems must be in place as well. For example, dysfunction in higher brain centers (i.e., Dorsal motor vagal nucleus, median raphe nucleus of the pons, and locus ceruleus) is important in irregularities of controlling patterns which govern swallowing and the migrating motor complex.[20,48]

α-synucleinopathy

As previously described, the presence of α-synuclein LB is one of the chief hallmarks of PD. While these LB have a large role in degeneration within the CNS, they are not restricted

by this, in fact being present in peripheral tissues and body fluids.[50] Apart from the SNpc, α-synuclein has been shown to have deleterious effects on the hypothalamus, sympathetic system, parasympathetic system, adrenal medulla, and neural plexi, innervating the gut and heart.[51] Moreover, LB-mediated lesions of the ENS have been shown to occur in the early stages of the disease, before CNS involvement.[49,52] One theory postulates that α-synuclein pathology begins in the ENS and retrogradely propagates to the CNS through preganglionic axons of the vagus nerve, then spreading to the implicated areas of the brain. This spread is thought to occur in a prion-like fashion between neurons. However, other evidence implies that α-synuclein pathology can coincide within the ENS and the CNS, and retrograde and anterograde (gut to brain and brain to gut, respectively) transmission can occur concomitantly. Regardless of the method or temporal arrangement of transport, LB and α-synucleinopathy have been implicated in stress within both the brain and gut.[53]

Gut microbiota alterations and Parkinson's disease

Alterations within the gut microbiota can result in changes of gut barrier function and intestinal permeability, which can influence not only local GI cells, and the immune system, but the ENS and resultingly the CNS as well. It has been thought that gut microbiota changes associated with intestinal inflammation may result in α-synuclein misfolding, but no causal relationship has been confirmed.[54,55] One direct mechanism in which the gut microbiota may contribute to PD is a promotion of susceptibility to inflammation and oxidative stress. It has been suggested that bacteria can enhance inflammatory responses to cerebral amyloids such as α-synuclein. α-synuclein and related amyloids can result in inflammation through toll-like receptor (TLR)-mediated glial cell activation. In PD specifically, upregulation of TLR2 signaling has been associated with neuroinflammation. Dysbiosis can lead to disruptions of the blood–brain barrier, further enhancing the described neuroinflammation.[56,57]

Specific alterations in the gut microbiota have also been described in the context of PD. For example, many PD patients show a reduction in *Prevotellaceae* bacteria and an increase of *Enterobacteriaceae*.[58] This shift in gut microbiota composition is associated with a decrease in mucin synthesis and increased intestinal permeability, which is consistent with the noted inflammatory patterns and promotion of protein misfolding.[9,59] In addition, small intestinal bacterial overgrowth (SIBO) has been described in a large proportion of PD cases. Interestingly, SIBO is associated with both GI and motor dysfunction. It is thought that dysbiosis in this fashion once again leads to increased intestinal permeability. SIBO has also been correlated with the accumulation of α-synuclein, further solidifying the role of dysbiosis in PD pathology.[60,61]

Specific pathogens have also been thought to have a potential role regarding the pathogenesis and development of motor symptoms. *Helicobacter pylori* (HP) is one pathogen that has had a controversial effect on PD development. The role of HP was first outlined due to an association of PD with gastric ulcers, in which HP is strongly implicated. HP has also been shown to hinder the absorption of levodopa (L-DOPA), which is the primary treatment for PD. The exact relationship of HP to PD development is still very early in the investigation process. Another pathogen that has been implicated in PD development is *Mycobacterium paratuberculosis* (MAP). Due to certain genetic mutations associated with PD, patients are highly susceptible to MAP infection, which is in turn associated with misfolding of proteins, i.e., α-synuclein.[20,62,63]

Investigative Methods

Several different investigative methods have been used to outline the effects of the gut microbiota further and build upon potential interactions between the gut microbiota and PD pathology.

Germ-free/gnotobiotic animals

Germ-free mice are mice that are free of all microorganisms, while gnotobiotic mice have been inoculated with a cocktail of one or more microorganisms, which is nonpathogenic.[64] One observation critical to drawing a connection between the gut microbiota and neurodegenerative diseases is the changes in neurotransmitter levels within germ-free mice compared to controls. Germ-free mice display roughly twice the amount of DA, and an increase in the turnover of DA, norepinephrine, and 5-HT.[65,66] Additionally, D1 DA receptor gene expression was elevated in the hippocampus and reduced in the striatum and nucleus accumbens of germ-free mice. As DA and, to a lower extent, norepinephrine and 5-HT are significantly implicated in PD pathogenesis, these alterations hint at a potential role of the gut microbiota in modulating factors related to the disease.[64]

Antibiotics

Various antibiotics have also been shown to confer neuroprotective and neurodegenerative effects in various PD models. For instance, minocycline (a broad-spectrum tetracycline antibiotic) has been shown to prevent neurodegeneration of nigrostriatal dopaminergic neurons and also prevented depletion of DA within the striatum and nucleus accumbens in MPTP PD mouse models.[67] Furthermore, in several trials, minocycline was reported to have several anti-inflammatory and antioxidant properties. Contrastingly, some studies have reported a neurodegenerative effect for minocycline. However, the overwhelming evidence points to a protective role.[68] One potential pathway through which minocycline may exert its therapeutic effect could be through reduction of the Firmicutes/Bacteroidetes ratio, consequently affecting PD through the gut microbiota–brain axis.[69] Ampicillin is another example of an antibiotic thought to have a potential role in modulating PD through the gut microbiota–brain axis. It has been shown that ampicillin confers neuroprotective effects as well, increasing the levels of tyrosine hydroxylase, D1 receptors, and D2 receptors.[70] A specific cocktail of antibiotics (consisting of neomycin, metronidazole, and polymyxin B) resulted in reduced

locomotor activity, thought to be associated with the altered ratios of bacterial species seen following treatment.[71]

Probiotics

Administration of probiotics, the "good" bacteria of the system, can have several beneficial effects, including aiding in PD. For example, Bacillus sp. JPJ has been shown to produce L-DOPA from L-tyrosine *in vitro*, which can consequently be converted to DA in the presence of DOPA decarboxylase.[72] Another interesting method that has only recently become a focus of research is the role of microbiota-produced vitamins in preventing inflammation. Vitamins which have been shown to confer positive effects include Vitamin E (potent antioxidant, preventing oxidative stress), Vitamin D3 (preventing deterioration in PD patients), riboflavin (shown to improve motor capacity in PD patients), and Vitamin B6 (low levels associated with increased risk of PD). In this manner, probiotics could lead to increased levels of these beneficial vitamins, directly influencing PD outcomes. Conversely, a lack of probiotics could lead to a potential deficiency, contributing to PD.[73,74]

Fecal microbiota transplant

Fecal microbiota transplant (FMT) is the technique wherein the gut microbiota is restored through the delivery of fecal matter of a healthy donor to the GI tract of the patient.[75] Interest in FMT in connection with PD was first piqued due to the several GI-related comorbidities of PD such as constipation, against which FMT was known to be effective. Interestingly, FMT was also shown to aid in the treatment of neurological symptoms, and thus several underlying mechanisms were proposed, further connecting the GI, gut microbiota, and PD. Currently, some of these mechanisms are thought to be direct communication through the vagus nerve, changes in the metabolism of neurotransmitters, immunomodulation, and production of active metabolites. Exact mechanisms relating to each pathway have yet to be described; however, it is known that the gut microbiota has effects through each one, extending plausibility to their role in PD modulation.[76]

Future Directions

The current body of literature regarding gut microbiota-mediated onset of PD is very preliminary, with lots of studies describing potential associations, and postulating potential mechanisms for the associations which are described. Very few studies have pinpointed specific pathways for a gut microbiota-centric etiology of PD. Furthermore, many clinical studies reporting such associations consist of limited samples. As such, many areas in this field require further studies to solidify connections and establish more precise mechanisms.

α-synucleinopathy

One specific area that remains in question with regard to specific mechanisms is α-synucleinopathy and transmission through the vagus nerve. Currently, it is unclear as how the transmission occurs from the ENS to CNS, even though the vagus nerve is the most likely route. More importantly, whether this transmission is anterograde (CNS to ENS) or retrograde (ENS to CNS) is still not solidified from a temporal view. Discovering the temporal relationship of this process could have significant impact on both diagnosis and potential therapeutic options. For instance, if a discovery of primarily retrograde transmission was made, this would display the potential for early detection and diagnosis of PD through the gut and potential α-synucleinopathies in the area. Also, therapeutically, the use of retrograde transmission could be manipulated to potentially have healing effects on the organism in question.

Microbiota colonies at risk

Furthermore, ratios of bacteria colonization within the gut microbiota associated with PD are widely inconsistent within the body of literature. There have been reports of different species and ratios of species leading to either neuroprotective or neurodegenerative effects of PD; however, inconsistencies still exist. Discovery of specific colonies or ratios of bacteria could also further improve diagnostic techniques, as early PD cases could be detected through this fashion. More importantly, specific pathways and effects exerted by different forms of the gut microbiome need to be discovered. Currently, there are various hypotheses on how different strains exert their effect and many associations have been made by different ratios and their neuroprotective or degenerative role, though specific pathways have not been outlined. Once again, testing the various hypotheses to elucidate specific mechanisms could be helpful in describing the gut microbiota-related etiology of PD.

Microbiota-produced vitamins/metabolites and specific effects

Another area of investigation that could have significant therapeutic implications includes production of vitamins and other metabolites by the gut microbiota. As was described, the gut microbiota can be involved in the production of various vitamins (e.g., Vitamin E), which confer protective effects against degeneration seen in PD. Still, how these effects are precisely mediated and how the vitamins themselves influence PD has not been elucidated. Additionally, the role of microbiota metabolites has been well studied in the context of local inflammation and drug metabolism, so it may be promising to study potential metabolite interactions in the context of PD.

Conclusions

The gut microbiota plays an essential role in the normal function of the human system, having critical roles in nutrient metabolism, drug metabolism, and immunomodulation among others. However, in states of dysbiosis, the gut microbiota could have diverse effects on the body, leading to pathology that is not limited to the GI system, as was traditionally thought. One pathology which is associated with dysbiosis is PD, which is primarily thought to work through an inflammatory process linked to the gut–brain axis. Due to the novel nature of these associations, specific pathways implicating the gut

microbiota in PD etiology have not yet been elucidated. Future research should examine specific pathways regarding α-synucleinopathy, specific gut microbiota colonies which impact PD, and the potential for gut microbiota metabolites to work in a preventative manner.

Authors' contribution

AE carried out the literature review and drafted the manuscript, MS revised the manuscript and provided insight as clinical gastroenterologist, MAH reviewed and analyzed the data as a pathoimmunologist, YA reviewed and analyzed the data as a neuroscientist, and MA supervised, evaluated, and helped to shape the final document. All authors reviewed and approved the final version.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

The article does not contain any human or animal experiments performed by any of the authors.

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