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REVIEWS

Neurodegeneration: A Tale of Microbes and Neurons

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Abstract

The gut-brain axis has emerged as a central paradigm in understanding the bidirectional relationship between the gastrointestinal microbiota and the central nervous system (CNS), particularly within the context of neurodegenerative disorders. This review synthesizes contemporary insights into how microbial dysbiosis and vagal pathways orchestrate critical processes in neurodevelopment and neurodegeneration. We dissect the multifaceted mechanisms by which microbial constituents, including lipopolysaccharides, bacterial amyloids, and amphiphilic compounds, penetrate host barriers such as the blood-brain barrier, contributing to neuroinflammation, protein misfolding, and neuronal dysfunction—hallmarks of diseases like Parkinson's disease, Alzheimer's disease, and multiple sclerosis. Although preclinical models present compelling findings, the need for longitudinal, large-scale clinical investigations remains critical. This synthesis underscores the gut microbiota as a therapeutic target within a precision medicine framework aimed at mitigating neurodegenerative disease onset and progression.

Keywords: microbiota, neurodegeneration, neuroinflammation, Parkinson's Disease

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INTRODUCTION

1. How microbes reach neurons – Blood brain barrier and inflammation

The interaction between microbes and the central nervous system (CNS) begins with understanding how pathogens circumvent the body's protective barriers, particularly the blood-brain barrier (BBB), and how inflammation contributes to this process. Our body needs many types of barriers to allow different homeostatic parameters and selective passage of molecules, compounds and cells in tissues and organs. Among all, blood brain barrier (BBB) is the tightest, and this has the understanding that the central nervous system (CNS) needs the best control of passage of substances to and from the capillaries, due to the restricted homeostasis intervals needed to function well[1]. Blood brain barrier functions are multiple, including protection from infectious agents. However, 'the intelligence' of simple life forms, such as microbes, viruses and prions is unexpected. For instance, viruses, such as Herpes Simplex Virus or rabies, can get into terminals of peripheral or cranial nerves and subsequently use the retrograde axonal transport to get into CNS, without any passage through the BBB[2]. Neisseria meningitidis, a common bacterium, can pass through BBB by endocytosis[3]. Intracellular transport nicely illustrates the trojan horse model, valid, for instance, for P. Falciparum[4]. However, infectious invasion can take place outside BBB, through subarachnoid space, choroid plexus, venous sinuses or cribriform plate. Therefore, infectious invasion of CNS is, unfortunately, still possible, regardless of BBB health and integrity. On other hand, BBB alterations occur with age and with neurodegeneration. Further on, in a vicious cycle, neurovascular units are affected when both infectious agents and neurodegeneration seeds are co-existing in place[5]. More to know, is that abnormal peptides, such as A-β, are synthetised and delivered to the brain tissue in response to infection[6]. The question remaining, for the start, is what damage is exactly doing an infection to the brain? Is it only BBB-mediated or is it systemic.

2. Inflammation and dysmetabolism affect brain function

Infections can affect CNS in multiple ways – not just directly, through CNS invasion. There are, actually, at least three ways an infection can affect brain/CNS function. First way is the direct way, easy to understand – such as HIV, it passes BBB, and gives a diversity of pathology – Borrelia, Koch bacillus, Treponema pallidum – the same old story[7]. However, besides this mechanism, we have a lot of infections causing neurological problems through an autoimmune mechanism. Our body is able to synthetise antibodies against a microbe or virus, but in a significant proportion of cases this antibody will attack self-structures, including CNS, based on structure homology. A classic example is given by the autoimmune encephalitis or myelitis[8]. This mechanism is important and underrecognized by physicians, and is treatable with IG IV or plasma exchange. Moreover, an infection give rise to metabolic changes. We plenary saw this in COVID-19 era. When oxygen saturation goes down to 50% is it unexpected to have neurological signs, such as memory problems and disorientation? We guess no. Inflammation is important for many life processes. Good and bad, as all things. However, inflammation is a risk factor for both cerebrovascular diseases[9] and for neurodegeneration[10].

THE GUT-BRAIN AXIS

The Vagus Nerve: A Bridge Between the Gut and the Brain

The gut-brain axis (GBA) has emerged as a fundamental concept in neuroscience, emphasizing the dynamic crosstalk between the gut microbiota and the central nervous system (CNS)[11]. This bidirectional communication occurs through various mechanisms, including neural pathways (such as the vagus nerve), immune signaling, and microbial metabolites[12].

In recent years, advances in microbiome research have reshaped our understanding of neurological disorders. Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), and psychiatric conditions such as anxiety, depression and autism spectrum disorder (ASD) have been linked to alterations in gut microbiota composition[12]. Experimental and clinical studies demonstrate that gut bacteria influence blood-brain barrier integrity, neurotransmitter turnover and regulation of synaptic-associated proteins, and reinforcing the hypothesis that targeting the gut microbiota could represent a novel therapeutic avenue for neurodegenerative diseases[13,14]. Despite significant advancements, several gaps remain in understanding how gut microbiota-driven mechanisms contribute to neurodegeneration. For instance, the directionality

of these interactions – whether dysbiosis is a cause or consequence of disease – remains an active area of investigation[15]. Additionally, while preclinical studies support the role of gut bacteria in neurodegeneration, large-scale human trials are still needed to validate these findings[16].

Among the key components of the gut-brain axis, the vagus nerve serves as a crucial mediator of bidirectional communication between the gastrointestinal tract (GI) and the central nervous system (CNS)[17].

The enteric nervous system (ENS) consists of two main plexuses: the myenteric plexus, which primarily controls GI motility, and the submucosal plexus, which regulates enzyme secretion and blood flow in the gut. The vagus nerve interacts with these plexuses to fine-tune digestive processes[17].

However, beyond digestion, the vagus nerve is increasingly recognized as a key link between gut microbiota and the brain, influencing neurotransmitter activity, neuroinflammation, and cognitive function[18,19]. Recent studies suggest that gut-derived signals, including microbial metabolites, can modulate brain function via vagal pathways, implicating this mechanism in various neurological and psychiatric disorders such as anxiety, depression, and neurodegenerative diseases like Parkinson's disease or anxiety disorder (PD)[19,20].

The following sections will examine the mechanisms through which the vagus nerve mediates gut-brain interactions, focusing on neurotransmitter regulation, microbial stimulation, and its implications in neurodegenerative conditions.

Microbial-derived compounds can directly interact with vagal afferents, particularly when intestinal barrier integrity is compromised. For example, lipopolysaccharides (LPS), key components of bacterial cell walls, can activate vagus nerve fibers through Toll-like receptor 4 (TLR-4), thereby triggering inflammatory responses[13,21]. Additionally, Jameson et al demonstrated that microbiome-dependent short-chain fatty acids, bile acids, and 3-indoxyl sulfate stimulate vagal activity in a receptor dependent manner[22].

Apart from direct stimulation, vagal activity can also be influenced indirectly through enteroendocrine cells lining the gut epithelium[23]. These cells release hormones and signaling molecules in response to gut microbial activity, which in turn modulate vagal activity[23]. For example, cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) – both involved in satiety regulation and gut motility – bind to receptors on vagal afferents, transmitting gut-derived signals to the CNS[23]. This mechanism highlights how the gut can influence brain function through endocrine signaling, further reinforcing the role of the vagus nerve in gut-brain communication[23].

Several experimental studies suggest that gut microbes can influence vagal signaling, with implications for cognitive and emotional processes. For example, ingestion of Lactobacillus rhamnosus strains has been shown to regulate emotional behaviour with anxiolytic effects. It acts through modulation of central GABA receptor expression, receptors implicated in anxiety behaviors via the vagus nerve in a regional dependent manner[24].

Similarly, Buffington et al demonstrated on mice studies that Lactobacillus reuteri is significantly reduced in offspring of mothers undergoing a high fat diet[25]. This diet impacted social behaviour in offspring and reintroduction of Lactobacillus reuteri improved social deficits.[25]

Similarly, Bifidobacterium longum has demonstrated anti-anxiety properties modulated via de vagus nerve in infectious colitis mice models [20]and changes in neural cell function. Methods Mice received dextran sodium sulfate (DSS, 3%. Interestingly, these effects are absent in vagotomized animals, demonstrating that the effect is mediated via the vagus nerve[20].

MICROBIOTA AND NEURODEVELOPMENT

Emerging research suggests that disruptions in microbiota during early development may set the stage for neurodegenerative processes later in life[13,26]. Alterations in early-life microbial colonization have been linked to persistent immune dysregulation, neuroinflammation, and synaptic abnormalities – key factors in neurodegeneration[26]. Additionally, experimental models suggest that early-life dysbiosis can predispose individuals to later-life neurodegenerative pathology by influencing blood-brain barrier permeability, microglial function, and alpha-synuclein aggregation[27]. Given these findings, understanding the microbiota's role in neurodevelopment is essential for unraveling the mechanisms underlying neurodegeneration.

Traditionally, it was believed that an infant's gut is colonized during birth, with the intrauterine environment considered sterile[28]. However, more recent studies challenge this "sterile womb" hypothesis, with microbial

traces have been detected in the first-pass meconium, placenta and amniotic fluid, suggesting that the human microbiome may begin to form in the womb[28,29]. While the existence of a true in utero microbiome remains controversial, maternal microbiota undoubtedly affect fetal brain development through immune modulation and metabolic signaling, influencing processes such as neurogenesis, myelination, glial cell function, synaptic pruning, and blood-brain barrier permeability[30-32].

Studying the microbiota's role in the developing brain may contribute to unravel long-term effects of altered microbiota composition in both neurodevelopmental and neurodegenerative disorders. The interaction between the gut microbiota, immune system, and nervous system during development may play a role in shaping cognitive function and neuropsychiatric disease risk later in life[16,33].

The analysis of genes related to neurodevelopment, including those coding for neuronal and glial transcription factors, regulatory proteins, structural proteins, and molecules crucial for synaptic signaling, revealed differential regulation in germ-free and specific pathogen-free mice with normal microbiota fetuses[34]. Almost all genes related to synaptic signaling were downregulated in germ-free mice fetuses, indicating the significant role of microbiota in neurodevelopment. One important molecule involved in neurodevelopment that was significantly downregulated in germ-free fetuses is the cytokine CX3CL1 (fractalkine, neurotactin)[34]. In mice lacking the CX3CL1 receptor, deficiencies in synaptic pruning, signaling, and brain connectivity have been observed, impacting social behavior[35].

Thion et al. found that murine microglia undergo several differentiation phases, which they assessed using transcriptomic signatures and chromatin accessibility landscapes[36]. Both transcriptomic signatures and chromatin accessibility levels were influenced by the absence of maternal microbiota[36]. The maternal microbiota may prime fetal microglia for their postnatal role[36]. Among the regulated genes, Ly86 and Aoah play roles in response to LPS[36]. Thus, microglia from germ-free mice exhibited transcriptomic changes that may be linked to a more hypoactivated immune state[36].

Accumulating evidence suggests that microbiota plays a crucial role in neurogenesis[14]. Ogbonnaya et al. demonstrated that germ-free mice exhibit a different pattern of neurogenesis compared to conventionally raised mice[37]. Adult germ-free mice show increased hippocampal neurogenesis, especially in the dorsal hippocampus, a difference that does not change with conventional colonization after weaning[37]. This finding suggests that early-life exposure to microbiota has a lasting influence on neurogenesis[14,37].

Bridging the Gut, Neurodevelopment, and Neurodegeneration

While early-life microbial colonization plays a critical role in shaping neurodevelopment and immune system programming, disruptions in this delicate balance may have profound implications for long-term neurological health. Research suggests that early dysbiosis – imbalances in the gut microbiota – can contribute to chronic neuroinflammation, alter blood-brain barrier (BBB) integrity, and influence microglial function, which in turn may predispose individuals to neurodegenerative conditions such as Parkinson's disease (PD) and multiple sclerosis (MS)[38].

Beyond its role in development, the gut microbiota continues to interact with the nervous system throughout life. One critical aspect of this interaction is the ability of microbes to reach and influence neurons within the central nervous system (CNS). While the gut-brain axis provides several indirect pathways for microbial metabolites to influence brain function, recent evidence suggests that certain pathogens and microbial components may also breach physiological barriers, such as the BBB, and directly interact with neural tissues. This process raises important questions about how microbial infiltration, chronic inflammation, and immune activation contribute to neurodegeneration[39].

The following sections will explore the mechanisms by which microbes and their byproducts can reach neurons, impact immune responses, and influence neuroinflammation – key processes implicated in neurodegenerative diseases such as PD, Alzheimer's disease (AD).

THE ROLE OF MICROBIOTA IN MULTIPLE SCLEROSIS: A GUT-BRAIN PERSPECTIVE

The gut microbiota has been increasingly implicated in the pathogenesis of multiple sclerosis (MS), a chronic autoimmune disorder affecting the central nervous system (CNS)[40]. Studies have shown that patients with MS exhibit distinct gut microbiota profiles compared to healthy individuals, with alterations in the

abundance of specific bacterial taxa. These microbial changes can influence the immune system, promoting a pro-inflammatory environment that contributes to CNS autoimmunity[40].

Experimental models have demonstrated that gut microbiota can modulate the severity of MS. Germ-free mice are highly resistant to the development of experimental autoimmune encephalitis (EAE) and develop significantly attenuated EAE, an animal model of MS, showing reduced proinflammatory responses compared with conventionally colonized mice, suggesting that microbiota is crucial for disease development[41]. Furthermore, transferring gut microbiota from MS patients to germ-free mice has been shown to induce EAE, indicating that specific microbial communities can trigger autoimmune responses[40].

Mechanistically, the microbiota interacts with the host immune system through various pathways. Short-chain fatty acids (SCFAs), metabolites produced by gut bacteria, have been found to exert anti-inflammatory effects and promote regulatory T cell (Treg) differentiation, which is protective in MS[42]. Moreover, it was demonstrated that gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in experimental autoimmune encephalomyelitis mouse models, also reducing IL-10+ proportions[43].

Studies in germ-free mice have provided additional insights. These mice exhibit higher blood-brain barrier (BBB) permeability from early development through adulthood compared to pathogen-free mice with normal microbiota[13]. This increased permeability correlates with lower expression of tight junction proteins, such as occludin and claudin-5, which are essential for maintaining BBB integrity[13]. Remarkably, when germ-free adult mice were colonized with microbiota, their BBB permeability decreased, suggesting that gut microbiota influence BBB function via vagal pathways[13]. This increased permeability of the BBB may contribute to CNS inflammation according to the "outside-in" theory, which states that inflammation in MS begins in periphery and extends towards CNS[44].

Recent studies have investigated the disparities in faecal gut microbiota between individuals with MS and a control group. These results show an imbalance in the gut microbial composition of MS patients[45]. For instance, in relapsing-remitting MS patients, Chen et al. found declines in the Parabacteroides, Adlercreutzia, and Prevotella genera and increases in the Pseudomonas, Mycoplasma, Haemophilus, Blautia, and Dorea genera[46]. Jangi et al. have provided evidence of the impact of MS medication treatment on gut microbiota. Therefore, compared to untreated MS patients, those who received beta-interferon or glatiramer acetate treatment showed higher levels of Prevotella and Sutterella and lower levels of Sarcina[47].

The role of gut microbiota in MS is further supported by interventional studies. Probiotic supplementation has been shown to modulate gut microbiota composition and reduce inflammatory markers in MS patients, suggesting a potential therapeutic avenue[48]. Additionally, dietary interventions, such as intermittent fasting, have been proposed as strategies to mitigate MS symptoms and progression through the potential of the diet to modify gut commensal bacteria and thus influence inflammatory responses[49].

MICROBIOTA AND ALZHEIMER DISEASE

Alzheimer's disease (AD) is a prevalent neurodegenerative condition characterized by cognitive decline and progressive neuroinflammation[50]. While the role of gut microbiota in multiple sclerosis (MS) has been well established in terms of immune modulation and neuroinflammation, emerging evidence suggests that microbiota-driven mechanisms may also play a crucial role in the pathogenesis of other neurodegenerative disorders, including Alzheimer's disease (AD)[51,52]. Both conditions share common pathological features, such as neural damage, infiltrating immune cells, blood-brain barrier (BBB) dysfunction, and immune system dysregulation, pathological features which may be related with alterations in microbiota[51,52].

Emerging evidence suggests that microbial dysbiosis in the gut can influence neuroinflammation and cognitive decline through the gut-brain axis. Several studies indicate that an altered composition of gut bacteria may contribute to systemic inflammation and oxidative stress, key factors in AD progression. For instance, microbial metabolites such as short-chain fatty acids (SCFAs) are known to modulate neuroinflammation and blood-brain barrier integrity, which are compromised in Alzheimer's patients[53]. Additionally, microbial byproducts like lipopolysaccharides (LPS) have been shown to exacerbate amyloid-beta deposition, a hallmark of AD pathology, by promoting chronic inflammation and immune activation within the central nervous system[54,55]. Minter et

al demonstrated-on AD mouse models that long-term broad-spectrum combinatorial antibiotic treatment altering the gut microbiota influences neuroinflammation and amyloid-beta deposition[56].

Further research has also highlighted the potential therapeutic implications of targeting gut microbiota to slow down or prevent Alzheimer's disease progression. Probiotic supplementation and fecal microbiota transplantation have been explored as strategies to restore healthy gut flora and reduce neuroinflammatory responses[57,58]. Mousel models of AD treated with specific probiotics have demonstrated improved cognitive function and higher hippocampal neuronal spine density[59]. Moreover, human studies are beginning to explore the associations between gut microbiota composition and AD risk, suggesting that early interventions aimed at maintaining or restoring microbial homeostasis could potentially delay the onset of neurodegenerative processes[60]. However, more clinical trials are needed to fully elucidate the therapeutic potential and long-term impacts of modulating gut microbiota in Alzheimer's disease patients.

LESSONS FROM PARKINSON'S DISEASE: CONNECTING THE VAGUS NERVE, MICROBIOTA AND NEURODEGENERATION

Alterations in vagal signaling have been implicated in neurodegenerative disorders, particularly Parkinson's disease (PD).

One of the earliest pathological signs of PD is the accumulation of alpha-synuclein aggregates in peripheral neurons, including those in the enteric nervous system (ENS) and the vagal dorsal motor nucleus[61]. This has led to the gut-origin hypothesis of PD, which proposes that pathological alpha-synuclein may propagate from the gut to the brain via the vagus nerve[61,62].

Epidemiological studies support this theory: patients who have undergone truncal vagotomy (surgical severance of the vagus nerve) show a significantly lower risk of developing PD[63]. Similarly, in experimental models, truncal vagotomy prevents the spread of alpha-synuclein aggregates to the brain and associated neurodegeneration[64].

The first study that highlighted the relationship between gut microbiota and PD was published in 2015 by Scheperjans et al, a metagenomic study in which fecal samples were collected from PD patients and healthy-control patients, the bacterial taxa were compared between the two groups and correlations were made between PD clinical phenotypes and the gut microbial composition[65]. Prevotellaceae, a family of bacteria that produces SCFA, such as butyrate, propionate and acetate which are known as the protectors of the gut health, were considerable reduced in PD patients[65]. Also, Enterobacteriaceae, Gram negative bacteria that contain LPS, which is an endotoxin that induces gut toxicity, were increased in PD patients and were correlated with gait impairment[65]. This study opened the possibility of the involvement of the gut microbiota in the pathogenesis and progression of PD. However, the study did not establish a causality, whether the change in the gut microbial composition was an initial step or a consequence of the disease, in which constipation is a major non-motor symptom[65].

Also, Keshavarzian et al, published in the same year a metagenomic study of the bacteria in the colonic mucosa and fecal microbiota were a reduce in protective bacteria such as Blautia, Coprococcus, Roseburia and Faecalibacterium and an increase in pro-inflammatory bacteria such as Akkermansia, Oscillospira, Bacteroides and Ralstonia were noticed in the gut of the PD patients in comparison to controls[66].

Another foundational study was the one published by Sampson et al, a mouse-model experimental study, in which alpha-synuclein-overexpressing mice were used and germ-free mice were compared with conventionally colonized mice[67]. The germ-free mice exhibited an alleviated motor syndrome in comparison with the mice colonized with gut microbiota[67]. Also, a transplantation of gut microbiota from PD patients to germ-free mice was performed and a more severe motor syndrome associated with increased neuroinflammation, measured by microglial activation and pro-inflammatory cytokines, were observed[67]. Although the study has certain limitations, such as an alpha-synuclein overexpression mouse model that does not replicate human PD pathology and the germ-free model in which a lack of microbial exposure from birth may modify the neurodevelopment, it is considered a strong experimental study, the first that showed that gut microbiota directly influences PD pathogenesis[67].

From this turning point, several studies explored the potential relationship between gut microbiota and PD. Another notable metagenomic study was published by Heintz-Buschart et al, where gut and nasal microbiota were compared to PD patients, idiopathic REM sleep

behaviour disorder (iRSBD), which is known as a disease with high-risk of developing PD and is considered a prodromal stage of PD, and healthy subjects[68]. The gut microbiota in PD patients was significantly different compared to the healthy subjects, while iRBD patients showed an intermediate transitional microbiota profile that overlaps with PD microbiota profile[68]. These findings suggest that the gut microbiota changes appear early in the clinical evolution of PD, they are not just a consequence of the treatment or of the severity of the motor or non-motor clinical syndrome, but could play a considerable role in the pathogenesis of PD[68]. Changes in the nasal microbiota were less significant than the changes in the gut microbiota, confirming the importance of the gastrointestinal site[68].

Aho et al, published a longitudinal study were PD patients had a persistent stable gut alteration over the course of 2 years in comparison to healthy controls, suggesting that gut dysbiosis is not just an episodic temporary phenomenon[69].

Once a relationship between gut microbiota changes and PD was established by the studies aformentioned, and having in mind what was already mentioned by the Braak hypothesis regarding the dissemination of alpha-synuclein from the intestinal tube to the brain through the vagus nerve, an important step to demonstrate the involvement of the gut microbiota in the pathogenesis of PD is to unveil the mechanism by which the microbes induce the formation of alpha-synuclein aggregates[27]. Several experimental studies showed that microbial compounds induce alpha-synuclein aggregation or an alpha-synuclein overexpression with a secondary aggregation process.

Curli fibers are amiloids produced by Escherichia coli in the process of biofilm formation that are able to cross-seed and induce aggregation of host's proteins[27]. Purified curli induces aggregation of alpha-synuclein in biochemical in vitro assays[27]. Sampson et al demonstrated in an alpha-synuclein-overexpressed mouse model that colonization with Escherichia coli-producing curli fibers favors alpha-synuclein aggregation in the gut[27].

Besides it's proinflammatory effects, LPS is a bacterial amphiphile. The hydophobic and hydrophilic components lead to the formation of micelles which can sequester specific proteins that would ultimately induce aggregation, if the proteins are prone to it[70,71]. The studies of Gorecki et al and Hurley et al showed that enteroendocrine cell lines treated with LPS have increased and altered intracellular alpha-synuclein[70,71]. Thus, the enteroendocrine cells may act as the initial site of alpha-synuclein aggregation, which is transmitted in a prion-like manner to neighbouring neuronal cells from the enteric plexus and, further, to the CNS via the vagus nerve[70,71].

Rhamnolipid is also a bacterial amphiphile produced by Pseudomonas aeruginosa. Fibrillation kinetics studies showed that purified rhamnolipid sequester alpha-synuclein inside the micelles and accellerates the aggregation[73].

Our recent in vitro study showed that both bacterial amphiphiles, rhamnolipid and LPS, increase alpha-synuclein intracellular levels in dopaminergic-differentiated neurons, thus favouring a subsequent alpha-synuclein aggregation[73].

Putting all these puzzle pieces together, we can conclude that microbiota plays a significant role in PD pathogenesis and the vagus nerve may serve as a conduit for neurodegenerative pathology, making it a potential therapeutic target for preventing or slowing PD progression, but still there are missing pieces that for now we cannot see the complete picture and all the complex mechanisms by which microbiota specifically take an action at the cellular and clinical level in PD patients are yet to be discovered.

CONCLUSION

The intricate relationship between the gut microbiota and the central nervous system (CNS) has emerged as a pivotal element in the pathogenesis and progression of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis. This review highlights how microbial metabolites, neuroimmune modulation, and the vagus nerve converge at the gut-brain axis to influence neurodevelopment, neuroinflammation, and neuronal homeostasis. Experimental and clinical evidence points to gut dysbiosis as a significant contributor to both the initiation and exacerbation of neurodegenerative processes, mediated by alterations in microbial composition, systemic inflammation, and breaches in blood-brain barrier integrity.

Additionally, this synthesis underscores the pathogenic role of microbial byproducts – including lipopolysaccharides, bacterial amyloids, and amphiphilic compounds – in the misfolding and aggregation of neuronal proteins such as alpha-synuclein, particularly in Parkinson's disease. The reviewed studies advocate

for a paradigm shift, positioning the gut microbiota not merely as a bystander but as an active modulator of neurodegenerative cascades.

Nevertheless, while preclinical data are compelling, further human studies are necessary to fully delineate causative pathways and therapeutic windows. Decoding the microbial signatures and host-microbiota interactions specific to each neurodegenerative condition will be critical for developing targeted, personalized interventions that leverage the gut-brain axis as a therapeutic frontier.

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