Gut Microbiome–Brain Crosstalk in Neurodegenerative Diseases

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The gut–brain axis (GBA) is a complex interactive network linking the gut to the brain. It involves the bidirectional communication between the gastrointestinal and the central nervous system, mediated by endocrinological, immunological, and neural signals. Perturbations of the GBA have been reported in many neurodegenerative diseases, suggesting a possible role in disease pathogenesis, making it a potential therapeutic target. The gut microbiome is a pivotal component of the GBA, and alterations in its composition have been linked to GBA dysfunction and CNS inflammation and degeneration. The gut microbiome might influence the homeostasis of the central nervous system homeostasis through the modulation of the immune system and, more directly, the production of molecules and metabolites. Small clinical and preclinical trials, in which microbial composition was manipulated using dietary changes, fecal microbiome transplantation, and probiotic supplements, have provided promising outcomes.

gut microbiome gut–brain axis neurodegenerative diseases

1. Introduction

The gut–brain axis (GBA) refers to a complex network of bidirectional interactions between the gut microbiome and the central nervous system (CNS). The GBA involves multiple biological systems and is crucial in maintaining the overall body homeostasis [1]. Signals travel from the gut to the CNS and vice versa, either directly through the autonomic nervous system or indirectly through metabolites and chemical transmitters [1][2]. Both of these interactions can modulate and be influenced by the gut microbiome composition. The GBA has recently attracted interest due to its emerging role in mediating health and disease and potential use as a therapeutic target. The gut microbiome impacts many aspects of brain development and function, including microglia and astrocyte maturation and polarization, blood–brain barrier (BBB) formation and permeability, neurogenesis, and myelination [3][4][5][6][7][8][9]. GBA disruption may participate in the pathophysiology of several brain disorders, including neurodegenerative diseases [5][10][11][12]. However, controversy exists surrounding the extent and the exact mechanisms through which an altered gut microbiome may influence the development of CNS inflammation and degeneration.

2. The Gut Microbiome and Cognition

Microbiome composition is age-sensitive, and humans show marked differences in microbial profiles during infancy, adolescence, adulthood, and aging [13][14][15]. Many factors shape the developing microbiome: Genetics

[16], stress [17], mode of birth [18], diet [19], medication [20], and the environment [21]. Before birth, bacteria present in the placenta, amniotic cavity, umbilical cord, and meconium start to shape the characteristics of the future microbiome [22].

After birth, and during the first years of life, the gut microbiome of infants experiences significant changes, mainly influenced by feeding patterns (breast vs. artificial milk and, later, solid food). However, diet remains the main determinant of the gut microbiome composition in adults.

The gut microbiome has an intrinsic role in aging-related cognitive impairment. The dysbiotic status, characteristic of the aging microbiome, influences cognition through multiple pathways. The prevalence of bacteria considered proinflammatory, at the expense of more immunoregulatory microbial populations, can promote the release of pro-inflammatory cytokines and bacterial toxins, inhibit the transmission of the regulatory neural signal via the vagus nerve, and suppress the production and release of microbial metabolites and hormones [23][24].

From a neuropsychological point of view, several studies found a correlation between the gut microbiome composition and performance on cognitive tests (motor speed, attention, memory). For example, the relative abundance of *Actinobacteria* phylum has been linked to better performance in tests of attention, working memory, and paired-associate learning tasks [25]. In a mouse model, the administration of two *Bifidobacterium* strains improved memory and learning [26]. In humans, the administration of B. longum for 4 weeks was associated with reduced stress and improved visuospatial memory performance [27]. However, in another study, administration of the probiotic *Lactobacillus casei* Shirota to a cohort of healthy middle-aged subjects determined an improvement in mood but a parallel slight decrease in memory performance in neurocognitive tests [28]. Therefore, it is currently far from clear whether supplementation with psychobiotics, i.e., probiotics with an effect on the CNS, can exert any consistent effects on cognition in humans.

Furthermore, many of the benefits observed in learning and memory after the administration of probiotics occurred alongside reductions in biomarkers of stress (glucocorticoids) or inflammation (proinflammatory cytokines) [27]. Both glucocorticoids and proinflammatory cytokines impair cognitive performance under numerous conditions [29]. As stated above, dysbiosis is associated with impaired gut barrier function that allows bacteria or bacterial products to infiltrate into systemic circulation [30]. The resulting inflammatory states have been associated with behaviors such as social isolation, depression, apathy, and attentional impairments.

3. The Gut Microbiome and Parkinson’s Disease

Parkinson’s disease (PD) is a progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra and striatum, with abnormal accumulation of α-synuclein in the brain. The main symptoms of PD are resting tremors, stiffness, bradykinesia, and postural instability [31]. With disease progression, cognitive decline might ensue [32]. In addition, non-motor symptoms such as behavioral changes, sleep disorders, and gastrointestinal and autonomic dysfunction may precede the motor symptoms [33]. More than 80% of patients with PD experience gastrointestinal symptoms [34]. As in other neurodegenerative diseases, PD has been

associated with inflammation, specifically the inflammatory state resulting from the senescence of the immune system, defined as inflammaging [35]. In 2003, Braak and collaborators introduced the hypothesis that PD originates in the gut [36] and dysbiosis and gut inflammation are now considered important contributors to the disease pathogenesis [37][38]. Inflammatory responses have been described in the colonic tissues of animal models of the disease, including the elevation of proinflammatory cytokines and chemokines such as TNF-α, IL-1b, and leukocyte infiltration and activation [39][40]. In people with PD, serum levels of calprotectin, a marker of intestinal inflammation, were reported elevated compared to healthy controls (HCs) and correlated with monocyte count in the peripheral blood [41]. In another study, calprotectin, alpha-1-antitrypsin, and zonulin were also increased in people with PD [42]. Studies focused on gut microbiome changes in people with PD described a significant increase in the proinflammatory bacteria *Ralstonia, Akkermansia, Oscillospira*, and *Bacteriodes* [43]. *Bacteroides* and *Verrucomicrobiaceae* abundance have also been associated with plasma TNF-α and IFN-γ levels, respectively [44]. Another consistently reported alteration in PD patients is a decrease in *Roseburia* abundance [12]. *Roseburia* can enhance intestinal barrier function and reduce intestinal inflammation by upregulating antimicrobial peptide genes and toll-like receptor (TLR)-related genes, such as *TLR5*, and downregulating the NF-kB pathway [45]. Consistently, sigmoid mucosa biopsies obtained from patients with PD showed an increase in the expression of TLR4 mRNA compared to HCs [46]. In the rotenone mouse model, loss of the *TLR4* gene significantly improved intestinal barrier integrity and reduced intestinal and CNS inflammation, α-synuclein aggregation, and dopaminergic cell loss in the substantia nigra, thus alleviating the impairment of motor function [46].

Several animal studies have reported the spread of α-synuclein pathology from the gut to the brain, and pathological changes in the CNS can be observed after the injection of α-synuclein into the intestinal wall [47][48][49]. However, the exact route through which pathological deposits of α-synuclein may spread to the brain remains vastly hypothetical. According to Braak's original hypothesis, environmental factors may contribute, triggering the pathological process via the olfactory bulb or the intestinal nerve plexus [50]. Supporting this theory, vagotomy can prevent the transmission of pathological alpha-synuclein to the CNS in animal models [48].

4. The Gut Microbiome and Alzheimer's Disease

AD is the most common cause of cognitive decline worldwide [51]. It is characterized by the deposition of Amyloid beta (Aβ) plaques and hyperphosphorylated tau protein tangles, leading to neuroinflammation, synaptic dysfunction and, ultimately, neuronal loss [51]. As with PD, AD pathogenesis has also been linked to GBA dysfunction and increased intestinal inflammation [52]. The evidence of the possible role of the gut microbiome in AD pathogenesis came from the mouse model of the disease. GF APPPS1 mice showed a reduction in Aβ pathology compared to specific pathogen-free (SPF) mice [53]. Moreover, some recent studies have reported an altered gut microbiome composition in people with AD compared to HCs [10][54][55][56]. Aging itself impacts the gut microbiome composition, favoring proinflammatory bacteria, such as *Bacillus fragilis, Bacteroides fragilis*, and *Faecalibacterium prausnitzii*, to the detriment of more immune-regulatory bacteria [57]. Indeed, in patients with evidence of amyloid deposition, an increase in the proinflammatory taxa *Escherichia* and *Shigella* was associated with an increase in peripheral inflammatory markers such as interleukin-1β, NLR Family Pyrin Domain Containing

3, and C-X-C Motif Chemokine Ligand 2 (IL-1β, NLRP3, and CXCL2) [54][55][58]. The alterations most consistently reported by other studies include a decrease in *Firmicutes* and *Bifidobacteria*, together with an increase in *Proteobacteria* and *Enterobacteria* [54][55][58]. However, the results regarding *Bacteroidaceae* abundance seem to be less reproducible, with studies reporting either a decrease [59] or an increase [60], variably associated with alteration in *Actinobacteria* or *Prevotella*. The lack of consistency can be explained by the different geographical origins of the participants and the difference in comorbidities [61]. Interestingly, a pronounced difference in *Enterobacteriaceae* abundance between AD and MCI has been reported, suggesting the changes in gut microbiome composition might be gradual during disease progression [56].

As far as gut microbial products are concerned, an alteration in the gut's production of SCFAs, including butyrate, propionate, and acetate, has been repeatedly reported in patients with AD [57]. A decrease in SCFAs has been associated with increased epithelial leakage and bacterial translocation, with a consequent increase in circulating Gram-negative bacteria and LPS [62], microglia activation, and Aβ deposition in the CNS [63][64]. Moreover, a lower abundance of the butyrate-producing genus *Butyrivibrio* has been linked to a reduction in the intestinal expression of the transporter P-glycoprotein in AD patients [55]. Intestinal P-glycoprotein has been demonstrated to be essential for maintaining gut homeostasis and controlling intestinal inflammation [65]. Butyrate seems to have a protective effect against neuroinflammation in animal models of disease [66]. However, studies on the effect of SCFA supplementation reported contrasting results, with an even higher Aβ burden after treatment with butyrate in one study [63]. Besides acting locally, gut-derived metabolites can penetrate the CNS [67]. Elevated levels of trimethylamine N-oxide have been reported in people with AD and MCI compared to HCs and are correlated with Aβ and p-tau levels [68].

Lastly, as outlined in the previous paragraph, strains of bacteria derived from the gut microbiome can produce amyloids and favor Aβ peptide aggregation [57]. The proteins curli, TasA, CsgA, FapC, and phenol soluble modulins produced by *E. coli, B. subtilis, S. typhymurium, E. fluorescens*, and *S. aureus*, respectively, are only some of the bacteria-derived amyloids with the ability to promote the formation of Aβ oligomers and fibrils in vitro [69]. Bacterial-derived amyloids can act in concert with other bacterial-derived products, such as LPS, to trigger inflammation and increase Aβ deposition in the CNS, as it has been extensively demonstrated in animal models of AD [70][71][72].

5. The Gut Microbiome and Amyotrophic Lateral Sclerosis/Frontotemporal Dementia

Compared to other neurodegenerative disorders, little evidence supports the implication of the gut microbiome in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTD).

ALS is a fatal neurodegenerative disease characterized by the progressive loss of motor neurons [73]. One of the most common mutations associated with familial ALS is found in the superoxide dismutase 1 gene (SOD1) [73]. By looking at humanized SOD1 mutated mice (G93A), researchers found that these mice had decreased intestinal integrity, increased intestinal permeability, and abnormal Paneth cells, an important cluster of cells implicated in autophagy host–pathogen interactions. Moreover, G93A mice showed an atypical intestinal microbiome, meager in

SCFA-producing bacteria such as *Butyrivibrio fibrisolvens* [74]. Interestingly, butyrate supplementation successfully restored intestinal eubiosis and prolonged G93A mouse life spans [75].

Besides SCFA, nicotinamide supplementation also helps the improvement of ALS symptoms in the mouse model. In particular, the lack of *Akkermansia muciniphila*, a bacterium that produces a high quantity of nicotinamide, has been associated with a worse clinical course, and nicotinamide supplementation produced a partial improvement. Notably, changes in the gut microbiome composition were reported in the mouse model before clinical onset, opening the possibility of using the gut microbiome as an early biomarker of disease. Unfortunately, studies on people with ALS led to inconsistent results, possibly due to differences in sample size and patient characteristics [76][77]. However, recent studies seem to agree that ALS patients show a noticeable change in the gut microbial structure when compared to healthy controls, consisting of the increased abundance of the *Bacteroidetes* phylum, together with a decrease in *Firmicutes* [78], *Roseburia intestinalis* and *Eubacterium rectale*, two dominant butyrate-producing species [79].

Frontotemporal dementia (FTD) is a term referring to a wide variety of syndromes, including the behavioral variant frontotemporal dementia and the non-fluent and semantic variants of primary progressive aphasia, each of which can also be accompanied by ALS [80]. Studies on the GBA in people with FTD are scarce and limited to the animal model of the disease. FTD is a multifactorial disease with a solid genetic contribution and a variable degree of environmental influence. The three most common genes involved in the development of the disease are Chromosome 9 Open Reading Frame (*C9ORF*)*72*, Microtubule-Associated Protein Tau (*MAPT*), and Progranulin (*GRN*). The expansion of *C9ORF72* is considered the most common genetic cause of FTD and ALS [81]. As with *GRN* mutations, another less common genetic cause of FTD, *C9ORF72* expansion, is always associated with TAR DNA binging Protein (TDP)-43 pathology. *MAPT* mutations are invariably associated with Tau pathology [80].

While the loss of *C9ORF72* function in humans is associated with neurodegeneration, C9ORF72 reduction or complete deletion in knockout mice (*C9orf72*$^{-/-}$) does not trigger ALS or FTD-like disease [82]. *C9orf72*$^{-/-}$ present an inflammatory phenotype characterized by cytokine storm, splenomegaly, and neuroinflammation [83]. Remarkably, antibiotic treatment or fecal transplantation from an anti-inflammatory environment-associated mouse phenotype was able to rescue the phenotype [83].

Finally, microbiome studies on *Drosophila* flies carrying the transgenic mutant human FTDP-17-associated tau showed reduced gut motility and subsequently increased gut bacterial load in aged tau transgenic compared to control flies [84].

6. The Gut Microbiome and Other Forms of Dementia

Alterations in the GBA have been reported in Lewy body dementia (LBD), Huntington's disease (HD), and Creutzfeldt–Jakob disease (CJD). LBD is associated with impaired control of gastrointestinal and cardiac functions that might be linked to the loss of cholinergic dorsal vagal nucleus (DMV) neurons. The degree of DMV cell loss has been found to be similar in LBD patients with or without gastrointestinal symptoms [85].

HD is an inherited neurodegenerative disease that causes progressive motor decline, cognitive dysfunction, and neuropsychiatric symptoms. In addition to the neurological decline and similar to LBD, HD is associated with gastrointestinal disturbances, nutrient deficiencies, gastritis, and weight loss [86]. As reported in PD, AD, and ALS, one study found lower alpha and beta diversity, indicating less healthy baseline richness and altered microbial gut composition in HD patients than HCs [87].

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of fatal neurodegenerative diseases affecting humans and animals. Studies from three decades ago showed how germ-free mice infected with prions have increased survival compared to conventional mice, suggesting a role of microbes in enhancing the disease [88]. Moreover, the prion disease mouse microbiome is significantly different from non-infected mice, alongside SCFA and bile acid production [89].

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