Seminars in Immunology 69 (2023) 101802

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

The gut-brain vascular axis in neuroinflammation

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ARTICLE INFO

Keywords:
Microbiota
Alzheimer
Parkinson disease
Major depressive disorders
General anxiety disorders
Gut-Brain axis
Leaky-gut

ABSTRACT

The multifaceted microbiota characterizing our gut plays a crucial role in maintaining immune, metabolic and tissue homeostasis of the intestine as well as of distal organs, including the central nervous system. Microbial dysbiosis is reported in several inflammatory intestinal diseases characterized by the impairment of the gut epithelial and vascular barriers, defined as leaky gut, and it is reported as a potential danger condition associated with the development of metabolic, inflammatory and neurodegenerative diseases. Recently, we pointed out the strict connection between the gut and the brain via a novel vascular axis. Here we want to deepen our knowledge on the gut-brain axis, with particular emphasis on the connection between microbial dysbiosis, leaky gut, cerebral and gut vascular barriers, and neurodegenerative diseases. The firm association between microbial dysbiosis and impairment of the vascular gut-brain axis will be summarized in the context of protection, amelioration or boosting of Alzheimer, Parkinson, Major depressive and Anxiety disorders. Understanding the relationship between disease pathophysiology, mucosal barrier function and host-microbe interaction will foster the use of the microbiome as biomarker for health and disease as well as a target for therapeutic and nutritional advances.

1. Introduction

The microbiota is a complex and various ecosystem which is mainly constituted by bacteria but includes viruses, fungi, protozoa and archaea. These microbes are fundamental players in maintaining our health by controlling host immunity [1] and by promoting intestinal barrier functions [2]. The communication between the gut microbiota and the brain occurs through multiple pathways, including the vagus nerve, immune system interactions, microbial metabolites, and the endocrine system [3–5]. The microbiota communicates with the brain through the production of neuroactive substances and the modulation of the gut immune system as well as the network of neurons of the enteric nervous system (ENS), that connect the gut and the central nervous system (CNS) via the vagus nerve. In particular, the gut microbiota produces bioactive compounds, including neurotransmitters, neuropeptides, and hormones, which act on the enteric and systemic nervous systems and can influence brain function and behavior [6–8]. Significant amounts of serotonin, a neurotransmitter regulating mood, appetite, and sleep, are synthesized by enterochromaffin cells in the intestinal epithelium. In the gut, enterochromaffin cells use tryptophan from dietary protein to synthesize serotonin. This process is regulated by the gut microbiota kynurenine synthesis pathway [9]. Imbalances in serotonin levels have been associated with various psychiatric disorders. Certain gut bacteria are capable of producing gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter that influences anxiety and stress responses [9].

The gut microbiota-brain axis is controlled by the systemic circulation equipped with various vascular and epithelial barriers such as the intestinal epithelial barrier (IEB), gut-vascular barrier (GVB), blood-brain barrier (BBB), choroid plexus vascular barrier (PVB) and blood-cerebrospinal fluid barrier (B-CSF). The mucosal barrier in the intestine is composed of a multilayered system which includes the mucus, the epithelium and the GVB. The latter is the most inner layer of defense constituted by endothelial cells connected by TJs and adherens junctions (AJs: catenin and cadherin proteins) and finely regulated for its permeability by the plasmalemma vesicle-associated glycoprotein-1

Abbreviations: AD, Alzheimer disease; AJ, Adherens junctions; FMT, fecal microbial transplantation; AD, generalized anxiety disorder; GVB, Gut vascular barrier; HPA, Hypothalamic–pituitary–adrenal; IBD, Inflammatory Bowel Diseases; IBS, Irritable Bowel Syndrome; LPS, Lipopolysaccharide; MDD, major depressive disorder; PD, Parkinson disease; PVB, Choroid Plexus Vascular Barrier; SCFA, Short chain fatty acid; TJ, Tight junctions.

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https://doi.org/10.1016/j.smim.2023.101802

Available online 7 July 2023

(PV-1) [10,11]. Maintenance of intestinal epithelial and vasculature structures is fundamental in promoting gut microbiota barrier homeostasis and in mediating the correct exchange of metabolites and molecules from the intestinal lumen to the systemic circulation. The relevance of the microbiota in the modulation of the vasculature of the CNS is evident in Germ free mice which exhibit elevated BBB and B-CSF permeability compared to specific pathogen-free (SPF) mice. This alteration is linked to decreased expression of tight junction proteins (TJs), including occludin and claudin-5 for the BBB and zonula-occludens 1 (ZO-1) for the B-CSF [12,13]. This impairment is strictly dependent on microbial signaling which can, through the colonization of germ-free adult mice with a SPF-derived gut microbiota, reduce BBB permeability and upregulate tight junction protein expression [13]. Moreover, the fermentation of dietary fibers by gut bacteria generates short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. These SCFAs can cross the BBB and influence brain function as well as regulate blood flow. The gut microbiota is implicated in modulating the integrity and permeability of the BBB and B-CSF. Specific microbial endotoxin, such as lipopolysaccharides (LPS), can induce inflammation and impact the integrity of BBB and PVB. Thus, the balance between the intestinal microbiota, immune cell signaling and vascular permeabilities of the gut and CNS are crucial for the maintenance of the functionality of the intestinal and cerebral barriers [3–5,11,14,13].

Microbial dysbiosis and the leaky gut are two of the main features reported in several intestinal disorders such as Inflammatory Bowel Diseases (IBD) and Irritable Bowel Syndrome (IBS).

Damage of the GVB allows microbes, microbial antigens and inflammatory mediators to enter the circulation causing low-grade systemic inflammation, which in turn can reach distal organs including the brain [11,14,15]. Indeed, due to the loss of intestinal mucosal homeostasis and increase of pro-inflammatory molecules, IBD and IBS, are considered as significant risk comorbidities for neurological diseases including Alzheimer (AD), Parkinson (PD) and behavioral diseases [16–20].

Our recent report demonstrates that, upon intestinal inflammation and GVB disruption, the cerebral endothelium of the choroid Plexus, which in physiological conditions is fenestrated and permeable to large (70 kDa) molecules coming from the systemic circulation, behaves as a Vascular Barrier (PVB), by closing its accessibility to inflammatory and bacterial molecules. Consistently, we detected the closure of the PVB also during systemic injection of lipopolysaccharide (LPS), the outer membrane endotoxin of gram-negative bacteria [14]. This highlights the existence of a GVB-PVB axis. which can be modulated by bacterial toxins. The GVB-PVB axis represents a fundamental caretaker in leukocyte trafficking and signaling between the intestine and the brain [21,22].

Thus, microbiota mediated intestinal dysregulation could lead to the loss of intestinal barrier function and the parallel establishment of the choroid plexus vascular barrier, resulting in distal neurological defaults. We do not know whether prolonged and chronic inflammatory stimuli derived from the dysbiotic, and overstimulated gut could mediate the inability of the PVB to control its permeability dampening the PVB-dependent brain protection program.

Here we want to summarize taxonomic and functional studies on the gut microbiota that are associated with intestinal and cerebral barrier dysfunction in neuro -degenerative and -psychiatric disorders.

2. The complex interplay between genetic and environmental factors in the etiology of neuro -degenerative and -psychiatric disorders

Alzheimer (AD) and Parkinson disease (PD) are the most two frequent causes of age-related dementia and are characterized by the disruption of neurons and their connections, which in turn lead to an irreversible and progressive cognitive decay. The pathophysiological process outlining the neurological impairment of AD and PD involves neuronal -oxidative tissue damage, -apoptosis, neuroinflammation. AD is associated with the development, accumulation and aggregation of amyloids including plaques of amyloid-β peptide (Aβ) in hippocampus, amygdala, entorhinal cortex, basal forebrain and cerebrospinal fluid. The formation of amyloid aggregates mediates the activation of microglia and astrocyte cells which in turn, activate the secretion of cytokines, lipids and free radicals and contribute to a pro-inflammatory CNS environment. PD is characterized by aggregates of misfolded α-synuclein in substantia nigra.

As regards neuro-psychiatric disorders we have focused on two of the most common mental health conditions: major depressive disorder (MDD) and generalized anxiety disorder (GAD). Also in this case, inflammation seems to play a sparkling role in driving these pathologies. Indeed, the systemic increase of inflammatory markers such as c-reactive protein (CRP) and IL-6 which is associated with a decrease of monoamine neurotransmitters (e.g., serotonin, noradrenaline, dopamine) and accumulation of tryptophan catabolites, are both involved in the impairment of monoaminergic system and CNS toxicity [23,24]. In MDD and GAD, the malfunctioning of glucocorticoid receptors is also reported, and their impairment is associated with hyperactivation of Hypothalamic–pituitary–adrenal (HPA) axis, damage of neurogenesis and reduction of hippocampal volumes and functions.

Presently, none of the mechanisms reported to be involved in the progression of AD, PD, MDD and GAD, are clearly associated with the etiology of these neurological disorders. In other words, the triggering factors inducing the activation of these mechanisms remain poorly understood.

Studies based on host genetic variants highlight a familiarity in neuro -degenerative and -psychiatric disease. The heritability is evaluated between 60 % and 80 % for AD [25] around 10–20 % for PD [26], and about 67 %/49 % for MDD/GAD [27]. However, genome-wide association studies were not able to explain most of the observed familiarity, unveiling the poor comprehension of the etiology of these diseases and suggesting a contribution of the environment. The discussion below, based on preclinical studies and clinical evidence, will help in the comprehension of a potential role of the microbiota in driving and boosting the progression of neuro -degenerative and -psychiatric disorders.

2.1. Leaky gut and microbial dysbiosis precede and boost the development of neurological diseases

Several clinical reports on PD patients highlighted colonic inflammation, intestinal dysfunctions and concomitant changes in fecal microbiota composition [28–30]. Interestingly, gut dysfunction of PD patients precedes for years motor symptoms [31,32].

The timing of intestinal dysfunction and microbial dysbiosis suggest that the loss of gut-brain axis homeostasis could contribute to the pathophysiology of the disease.

A role of the intestinal microbiota in the etiology of PD is shown in preclinical research whereby antibiotic administration and fecal microbial transplantation impact on the development of the disease. Sampson and colleagues treated αSynuclein-overexpressing (ASO) PD mice with a broad spectrum mix of antibiotics. The antibiotic treatment inhibited the loss of dopaminergic neurons in the compact substantia nigra, reduced the activation of microglia and ameliorated motor impairment [33]. The authors also reported that transplantation of ASO mice with microbiota from PD-affected patients, but not from control donors, enhanced the progression of PD including dyskinesia and abnormal intestinal functions [33].

To study also a possible beneficial contribution of the intestinal microbiota in protecting from PD progression, the effect of fecal transplantation of healthy microbiota (FMT) in a mouse model of PD induced by rotenone was analyzed. Following the administration of rotenone, mice showed a concomitant impairment of gastrointestinal functions

and behavior. The FMT from healthy microbiota was able to restore microbial eubiosis, intestinal barrier functions and reduced systemic inflammation and motor deficit. The effect of microbial transplantation was also evident in the brain, in which the impairment of the BBB and the reduction of dopaminergic neurons as well as neuro-inflammatory parameters were restrained [34], (Fig. 1, PD).

These data suggest that the gut-microbiota-brain axis could be a key factor in contributing to the development of PD but could be harnessed to protect from its progression.

MDD and GAD are also associated with co-existing intestinal manifestations such as the leaky gut and gastrointestinal pain [28,29], that are characteristic of several intestinal disorders such as inflammatory Bowel Diseases (IBD) and irritable Bowel Syndrome (IBS). Intriguingly, the latter are at greater risk for developing psychiatric conditions including anxiety and depression [35,36]. Thus, the correlation between IBS, IBD, depression and anxiety seem to be bidirectional.

One of proposed mechanisms which links the alteration of intestinal microbiota and the activation of the inflammatory response with neurological disorders is the expansion of pro-inflammatory bacterial components and the alteration of tryptophan catabolism which is responsible for the production of some neurotransmitters [37]. These conditions could lead to the loss of intestinal barrier functions and boost the release of circulating pro-inflammatory molecules, such as IL-6, IL-10 and tumor necrosis factor (TNF) and unbalanced neurotransmitter production [37,38]. The importance of pro-inflammatory molecules in triggering behavioral changes in preclinical models is reported by our and other groups [14,39–41], in which intestinal inflammation mediated by dextran sodium sulfate (DSS) colitis was associated with changes in behavior. Indeed, as we recently reported, DSS treatment leads to the passage of LPS and proinflammatory mediators within the systemic circulation driving the alteration of behavior and choroid plexus permeability [14]. We were able to show a dialogue between the gut and the brain which, if interrupted in the presence of gut inflammation, could lead to behavioral alterations and a drastic impairment of PVB-mediated permeability of the CNS. Vicentini and colleagues described that behavioral abnormalities were transferred through cecal microbiota transplantation into germ free and antibiotic treated mice confirming that microbial dysbiosis could lead to behavioral changes in colitis [41], presumably via the alteration of the PVB. Consistently, functional studies showed that fecal microbial transplantation from MDD patients in germ-free mice could recapitulate depression-like behaviors, supporting the hypothesis of a microbial dependent sustainment of MDD/GAD [42] (Fig. 1, MDD\GAD).

The last evidence supporting the gut-microbiota axis as a fundamental trigger for neurodegenerative disorders concerns some studies carried out in preclinical models of AD. The first study shows that the intestine is a reservoir for the amyloid-β protein. The familiar AD (FAD) transgenic mouse model, which overexpresses human amyloid precursor protein (APP) and preselinin-1 (PS1), showed that amyloid-β protein precursor accumulated not only in the brain but also, and earlier, in the gut of FAD mice [43]. The strict association between intestinal accumulation of the amyloid-β protein and the development of AD seems to be confirmed by the effects of the enteric administration of Aβ, which leads to AD-like phenotype including β-amyloidosis in brain parenchyma and cognitive impairment [44].

Evidence of an intestinal involvement is also supported by a transgenic mouse model of AD (Tg2576), that overexpresses the double mutated form of human APP695. These mice present an impairment of the intestinal function and enteric Aβ deposition before the detection of cerebral Aβ aggregation [45]. These studies highlight that enteric system

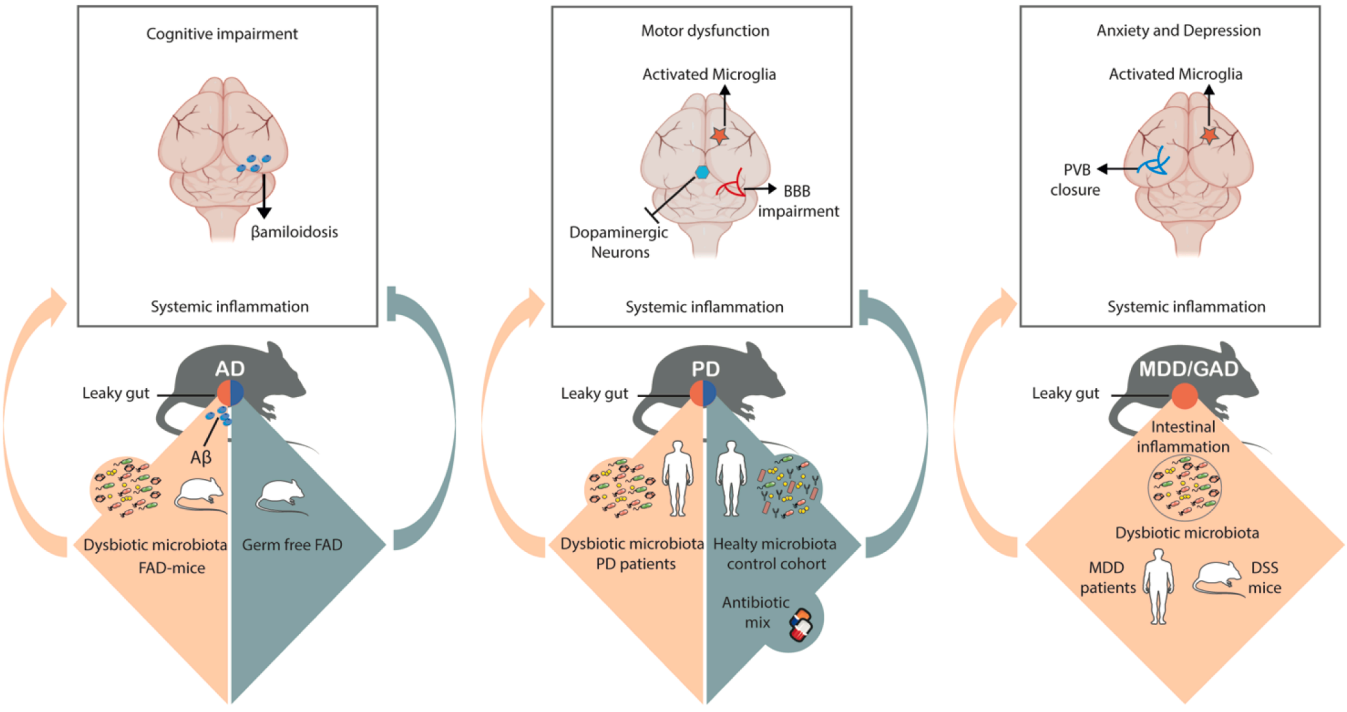

Fig. 1. Dysbiotic microbiota and leaky gut are involved in the development of neurological diseases. (AD) FAD and Tg2576 transgenic murine models of AD show impaired intestinal function and enteric Aβ deposition before the detection of cerebral Aβ aggregation. The reconstitution of the dysbiotic microbiota in Germ free FAD mice recapitulates the increase of cerebral amyloidosis. The crucial role of the microbiota is revealed by the radical reduction in development and accumulation of Aβ plaques in Germ free FAD mice. (PD) Schematic representation of the effect mediated by fecal microbiota transplantation from PD patients in ASO-, preclinical mouse models of PD. Recipient mice present with leaky gut before the development of neurological symptoms. The antibiotic treatment and FMT from healthy microbiota can repristinate gut barrier functions and reduce systemic inflammation, dopaminergic neurons, BBB impairment, microglial activation and motor dysfunction. (MDD/GAD) Anxiety and depression behaviors are observed concomitantly to the activated microglia and PVB closure in murine model of DSS-induced intestinal colitis. The FMT from MDD patients and DSS-treated mice donors to antibiotic treated and Germ-free recipient mice recapitulate the systemic inflammation, neural and behavioral impairments characterizing MDD/GAD.

dysfunctions and intestinal dysbiosis have to be considered as relevant factors involved in the etiology and pathogenesis of AD [46].

But what drives intestinal inflammation or dysfunction? Could it be linked to microbial dysbiosis? In both AD and PD patients, the gut microbiota is impaired in richness and diversity [47,48]. The reduction of microbial complexity shown in AD and PD mainly involves a significant decrease of Firmicutes/Bacteroidetes ratio at phylum level, together with a diminished amount of Actinobacteria [47–51]. Different studies also revealed a dysbiotic change peculiars to MDD/GAD phenotypes [37,41].

The alteration of fecal microbiota is also reported in preclinical models of AD, and it correlates with histological and behavioral manifestations of the disease [43,52,53]. The FAD mouse model also presents an altered microbiota suggesting that the presence of the mutated transgenes (AβPP and PS1), could select specific microbial strains. However, the alteration of the microbiota does not appear to be only a consequence of the disease. Indeed, Harach et al., reported the possible role of the intestinal microbiota as trigger of the etiology of AD with two fundamental preclinical pieces of evidence: i) The drastic reduction in development and accumulation of Aβ plaques in Germ free FAD mice [54]. ii) Reconstitution of the dysbiotic microbiota in Germ free FAD mice recapitulates the increase of cerebral amyloidosis [54] (Fig. 1, AD).

All this preclinical evidence on AD, suggests the possibility that the gut could bear the Aβ accumulation before the brain and this first event could foster the cerebral amyloidosis.

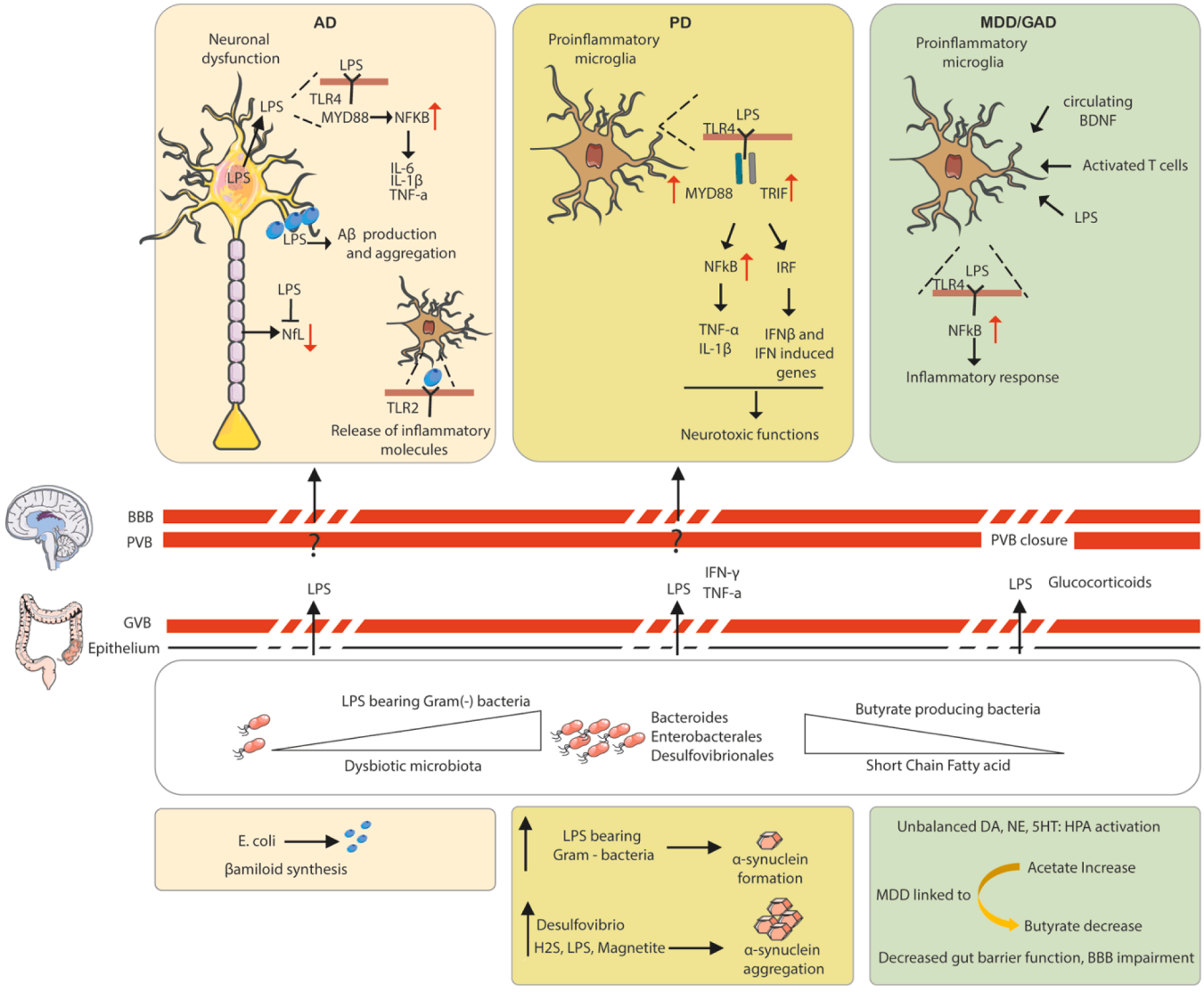

Fig. 2. Microbial mechanisms involved in the pathophysiology of neurological disorders.
The increase of LPS bearing bacteria and the reduction of SCFA producing bacteria are considered as crucial events involved in the disruption of intestinal barrier integrity. The passage of the LPS from the destroyed GVB-BBB axis is correlated to the AD, PD and MDD/GAD development. (AD) In particular, LPS produced by *E. coli* can promote synthesis and aggregation of Aβ amyloids and sustain the neuro-inflammatory process through the activation of TLR4 in neurons. The production of Aβ amyloids mediated by *E. coli* can lead to the activation of TLR2 expressed in the microglia and the release of inflammatory molecules. (PD) In PD pathology, the LPS of bearing gram negative bacteria can trigger the loss of intestinal barrier integrity and the accumulation of α-synuclein. Moreover, it can induce a proinflammatory phenotype of microglia and the release of cytokines and chemokines. (MDD/GAD) The expansion of Gram-negative bacteria including Enterobacteriaceae and *Desulfovibrio* causes a decrease in butyrate. The reduction of butyrate is associated to the loss of gut barrier function and BBB impairment. Moreover, the dysbiotic microbiota is associated with unbalanced DA, NE, 5HT metabolism which in turn activates HPA axis. The LPS together with the increase of circulating BDNF and activated T-cells mediate the induction of proinflammatory microglial phenotype, the activation of NfkB and inflammatory response.

3. Microbial mediated mechanisms involved in the development and progression on neuro- degenerative and -psychiatric disorders

3.1. Gram-negative bacterial LPS drives a pro-inflammatory environment

One of the most consistent result shared between neuro- degenerative and -psychiatric disorders is the increase of gram negative LPS bearing bacteria such as *Bacteroides*, Enterobacterales, *Escherichia/Shigella,* and *Desulfovibrio* pro-inflammatory species [40,42,43,47–50,55–63].

An intriguing possibility is that LPS, derived from the expansion of Gram-negative bacteria, could accumulate and through the alteration of intestinal barrier permeability, could reach the systemic circulation, activating a pro-inflammatory response not only locally but also at distal sites, including the CNS with different outcomes depending on the duration of the stimulus. The Enterobacteriaceae, including *Escherichia/Shigella,* have been reported to increase in feces of AD patients [55,64]. The expansion of *Escherichia coli* was significantly associated with the development of amyloid fibers both in AD and PD [65]. Different studies showed that the LPS produced by *E. coli* colocalized with amyloid plaques and demonstrated that it can help to build up myelin aggregates [64–69]. In PD the mechanism involved in LPS-mediated CNS inflammation involved the systemic release of IFNγ and TNFα cytokines [70,71]. This correlated with the activation of TLRs which in turn lead to the activation of key master regulators such as MyD88, TRIF, STAT5, IRFs and NF-κB, and could induce the pro-inflammatory M1 phenotype of microglia [72,73], (Fig. 2, PD). Also, in MDD/GAD gram-negative expansion and translocation of microbial-derived metabolites and LPS is reported to drive the activation of innate immune recognition receptors and the consequent inflammation of the CNS [60]. However, once administered intraperitoneally LPS could drive PVB closure [14] and this may lead to an anxiety-like behavior in mice. PVB closure could represent a sufficient condition for the development of an anxiety/depressive phenotype in preclinical mouse model, recapitulating the pathophysiology of MDD/GAD (Fig. 2, MDD/GAD). It is not known whether continuous release of LPS, and not just a spike, may instead lead to BBB impairment and neuroinflammation [74]. Further, fnctional studies reveal that enterotoxigenic *Bacteroides fragilis* secretes a neurotoxic form of LPS, which can enter the brain cell plasma membrane [75,76], inducing TLR4/MyD88/NF-kB signaling and inhibiting the expression of neurofilament light (NF-L), a cytoskeletal element involved in the maintenance of neuronal signaling and known to be downregulated within CNS neurons of AD patients (Fig. 2, AD).

3.2. Intestinal bacteria can trigger the production of amyloid fibers and a-synuclein

A role of the intestine and its associated microbiota in the accumulation of amyloid fibers has been proposed. Different studies showed that both β-amyloid and α-synuclein accumulated in the gastrointestinal tract and could reach the substantia nigra and striatum through the vagus nerve, suggesting that the enteric nervous system could favor the accumulation of these fibers in the brain [77–79].

Gram-negative sulfate-reducing bacteria of the genus Desulfovibrio, which are expanded in PD patients, can induce the oligomerization and aggregation of the α-synuclein protein [33] (Fig. 2, PD). In addition, the hydrogen sulfide produced by several Enterobacteriaceae and Desulfovibrionaceae can enter host cells, cause the release of cytochrome c protein from mitochondria into the cytoplasm, mediate the accumulation of cytosolic iron and reactive oxygen species, thus boosting α-synuclein synthesis [80]. Other than the ability of bacteria to induce the formation of α-synuclein, some bacteria such as *E. coli* can synthesize amyloid fibers (e.g., curli, CsgA). The amyloid fiber produced by *E.* coli can cross the intestine and the BBB reaching the CNS and promoting the accumulation of amyloid plaques and fibrils [67–69]. This causative relationship between E. coli and amyloid fibers is supported by the significant association between *E. coli* enrichment and the development of amyloid fiber in AD patients [81]. In parallel to the promotion of Aβ deposition, *Escherichia/Shigella* seems to be also involved in the recruitment of inflammatory cells within plaques in APP/PS1 transgenic mice [82]. The neuro-inflammatory process is sustained by the binding of amyloids secreted by *E. coli* to TLR2 microglial receptors which in turn cause the activation of microglia and the release of inflammatory molecules [69] (Fig. 2, AD). Thus, these data show that the expansion of a core of sulfate-reducing bacteria and Enterobacteriaceae leads to the alteration of mucosal host cell physiology by increasing the levels of intestinal stressors (including but not limiting to LPS, hydrogen sulfide and magnetite) and could trigger the synthesis and aggregation of α-synuclein protein and β-amyloid within mammalian cells or directly synthesize β-amyloid. Thus, it seems that intestinal bacteria have to be considered as reservoir for the direct or undirect production of pathologic fibers.

3.3. The Microbiota controls the synthesis of neurotransmitters and their precursors

The gut microbiota is also strictly connected with the modulation of the HPA axis. The HPA axis is a major neuroendocrine system that connects the hypothalamus, anterior pituitary and adrenal glands. The hyperactivation of the HPA system is caused by the deregulation of signal molecules including neuropeptides and neurotransmitters and it can lead to the development of stress-related behavioral disorders. The gut microbiota can modulate the production of neurotransmitters and the synthesis of metabolites or molecules used as precursors of neuropeptides. One example is the tryptophan catabolism involved in the synthesis of serotonin [also named 5-hydroxytryptamine (5-HT)].

Neurotransmitters such as 5-HT, dopamine (DA), and noradrenaline (NE) are involved in the modulation of gastrointestinal secretion and peristalsis as well as in behavior and are exhaustively linked to the pathophysiology of anxiety and depression. 5-HT is reduced in MDD and GAD patients [83]. Consistently, the direct supplementation of 5-HT as well as the administration of the tryptophan producer *Bifidobacterium infantis* significantly improved gut microbiota homeostasis in mice and rats with depression-like behaviors and resulted in positive effects on restoring the balanced concentration of SCFAs, brain-derived neurotrophic factor (BDNF) and NE in the brainstem [83,84] (Fig. 2, MDD/GAD).

Even though intestinal bacteria have been shown to produce a series of major neurotransmitters and precursors including 5-HT, DA, and NE and tryptophan (Strandwitz,2018), so far if and how these can reach the CNS is ill-defined. Divergent data on the capacity of 5-HT to cross the BBB [85,86] reveal the necessity to investigate the routes and pathways involved in CNS bioavailability of neurotransmitters produced in the gut, including the capacity to cross the major gatekeeper between the systemic circulation and the CNS: the choroid plexus.

3.4. The alteration of SCFAs could be involved in loss of gut mucosal homeostasis

Short chain fatty acids (SCFAs), including acetate, butyrate and propionate, are important metabolites produced by beneficial microbes. The intestinal microbiome of both PD and AD patients is characterized by the reduction of SCFA producing bacteria [6,87,56]. The fecal content of SCFAs is also modified in MDD patients [88].

The decreased concentration of SCFAs could be considered as an important factor involved in the loss of gut-brain homeostasis. SCFAs are key contributors in maintaining intestinal mucosal barrier homeostasis by the preservation of functional barrier properties and anti-inflammatory signals.

In PD patients, the role of SCFAs is well described; indeed, the decrease of SCFAs (butyrate), causes the loss of intestinal barrier

integrity, the consequential dump of LPS and other pro-inflammatory molecules in the systemic circulation and microglia activation [6,89]. Moreover, upon microbial dysbiosis and SCFAs decrease, the levels of circulating glucagon like protein 1 (GLP-1), a hormone secreted by enteroendocrine epithelial L-cells and involved in the control of neuroinflammation, are reduced. The SCFAs mediated secretion of GLP-1 is considered another possible mechanism by which the alteration of bacteria metabolites can drive the induction of pro-inflammatory pathways [90] and depressive symptoms in PD patients [51]. Moreover, butyrate can also cause epigenetic changes in the genome of neurodegenerative disorder patients. Methylation analysis on blood samples from PD patients and controls, showed a correlation between the modulation of butyrate-producing bacteria taxa and epigenetic changes in genes containing butyrate-associated methylation sites including blood leucocytes and brain neurons. Interestingly, these modified sites overlapped with genes altered both in psychiatric and gastrointestinal diseases [87].

Microbial derived SCFA composition correlates clinically also with neural activity and brain structure, as assessed by functional and structural magnetic resonance imaging [91]. Recently, Muller and colleagues analyzed the feces of MDD/GAD patients for the presence of SCFAs and compared SCFAs profile with nuclear magnetic resonance spectroscopy and self-reported depressive and gut symptoms. Depressive symptoms severity correlated positively with acetate and negatively with butyrate [88].

The suggested relevance of butyrate is reported also in AD patients in which the microbiome was reduced in butyrate-producing bacteria such as members of the *Butyrivibrio* (*B. hungatei* and *B. proteoclasticus*) and *Eubacterium* (*E. eligens* , *E. hallii* , and *E. rectale*), and this association was also confirmed by the decrease in microbial butyrate-coding genes in the AD patient's cohort [56]. All these data strongly suggest the importance of SCFA, and butyrate, in protection against neurological disorders by the stabilization of intestinal barrier properties. Different studies showed that some SCFAs such as butyrate, propionate and acetate can cross the BBB probably through the monocarboxylate transport system [92] generating a feedback inhibition on brain uptake [93]. However, as data in mice on the exact contribution of each SCFA are controversial, further studies are needed to point out the role of SCFA in the modulation of brain homeostasis. It will be interesting to extend this knowledge to the cerebral choroid plexus barrier to evaluate its role in controlling opening or closure of the PVB.

4. Therapeutic strategies to improve the host-microbe interaction in neurological disorders

Nowadays, studies matching metagenomic microbial analysis with functional assays are fundamental to select therapeutic candidate molecules which can target the AD, PD, MDD/GAD pathologies.

The target strategy could be carried out considering two important mechanisms involved in therapy: i) a direct effect of microbial release of molecules capable of reestablishing gut and cerebral barrier homeostasis and restoring metabolic and anti-inflammatory balance between gut bacteria and the host, or ii) an indirect effect mediated by a reshaping of the host microbiota.

4.1. Bifidobacterium as a possible therapeutic strategy for neuro -degenerative and -psychiatric disorders

In accordance with a diminished amount of Actinobacteria at phylum level [47,48] the genus of *Bifidobacterium* results decreased in AD patients [47]. A low detection of *Bifidobacterium* was also associated with worsening of PD symptoms [94].

To assess if *Bifidobacterium* could have a role in protecting against neurodegenerative disorders, its administration was tested in preclinical models of PD and AD.

The administration of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI in familiar AD transgenic mice exerted a therapeutic effect by the shutdown of pro-inflammatory pathways involved in the deposition of amyloids and inhibition of apoptosis [95]. In this model, the administration of probiotic *Bifidobacterium* was also able to increase the number of neurons positive for brain derived neurotrophic factor (BDNF) and improved the activity of synaptic scaffolding protein in the hippocampus of FAD mice when compared with control-treated FAD mice. Probiotic administration was also able to downregulate the expression of IL-17, IL-6 and NF-kB together with the inhibition of the downstream marker COX2. Also, Iba1 and Gfap, markers for microglial and astrocyte activation, significantly decreased. [95](Fig. 3, AD). The impact of *Bifidobacterium* on molecules involved in the pathophysiology of AD, was also described in the study of Abdelhamid et al. [96]. Upon administration of *B. breve* MCC1274 in WT mice the authors reported a reduction of the protein presenilin1, which in turn decreased the amount of Aβ42 in the hippocampus and the phosphorylated form of tau, leading to an attenuated microglial activation (Fig. 3, AD).

To shed light on possible indirect effects of Bifidobacterium mediated by a reshaping of the intestinal microbiota and its involvement in the amelioration of the AD phenotype, H. Kim et al. analyzed the effect of *Bifidobacterium* on microbial taxonomy. AD mice that received *B. bifidum* BNG4 and *B. longum* BORI reported an expansion of *Akkermansia, Faecalibacterium, Erysipelatoclostridium and Candidatus_Stoquefichus*. To test the direct effect of *Akkermansia muciniphila* on AD pathologies they used *Akkermansia* as probiotic. The administration of *Akkermansia* reduced the amyloidosis in the cerebral cortex of APP/PS1 mice [97] (Fig. 3, AD).

The treatment with Bifidobacterium seems to be effective in reshaping the host microbiota also in the murine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD [98]. The oral administration of *B. breve* CCFM1067 to MPTP-induced PD mice, was able to reduce intestinal microbial dysbiosis by decreasing the number of pathogenic bacteria (*Escherichia-Shigella*) and increasing the number of *Bifidobacterium* and *Akkermansia.* The production of SCFAs (butyrate and acetate) was also restored and this could explain the local and cerebral anti-inflammatory effect. Indeed, upon probiotic administration intestinal and blood-brain barriers were preserved. Additionally, the treatment with *B. breve* CCFM1067 was able to decrease the number of impaired dopaminergic neurons, inhibit hyperactivation of glial cells, reduce the oxidative stress and neuroinflammation [98], (Fig. 3, PD).

The probiotic administration of *B. longum* and *Lactobacillus helveticus* could also decrease anxiety [99–101]. The effect of *Bifidobacterium* in combination with other SCFAs producing bacteria was evaluated in MDD patients: a mix of 8 different strains including *Streptococcus thermophilus* (NCIMB 30438), *Bifidobacterium breve* (NCIMB 30441), *Bifidobacterium lactis* (NCIMB 30435 and 30436), *Lactobacillus acidophilus* (NCIMB 30442), *Lactobacillus plantarum* (NCIMB 30437), *Lactobacillus paracasei* (NCIMB 30439), and *Lactobacillus helveticus* (NCIMB 30440) was added to the standard of care treatment. Four weeks after probiotic administration, probiotic-treated patients showed a reduced putamen activation and a significant decrease of the Hamilton Depression Rating Scale (HAM-D) in the probiotics group [102], (Fig. 3, MDD\GAD).

These data show a huge potential of probiotics comprising different species of Bifidobacterium, as oral supplement therapy useful in modulating gut-brain axis homeostasis and slowing down the progression of neuro -degenerative and -psychiatric disorders.

4.2. Food derived bioactive molecules can be protective against neurodegeneration

Nowadays, it is increasingly demonstrated that diet represents a fundamental component in the maintenance of health via direct and indirect effects mediated by the modulation of the microbiota, immune cells and intestinal barrier functions. Fermentable oligo monosaccharides, a low-lactose diet, and medicinal food herbs could help to

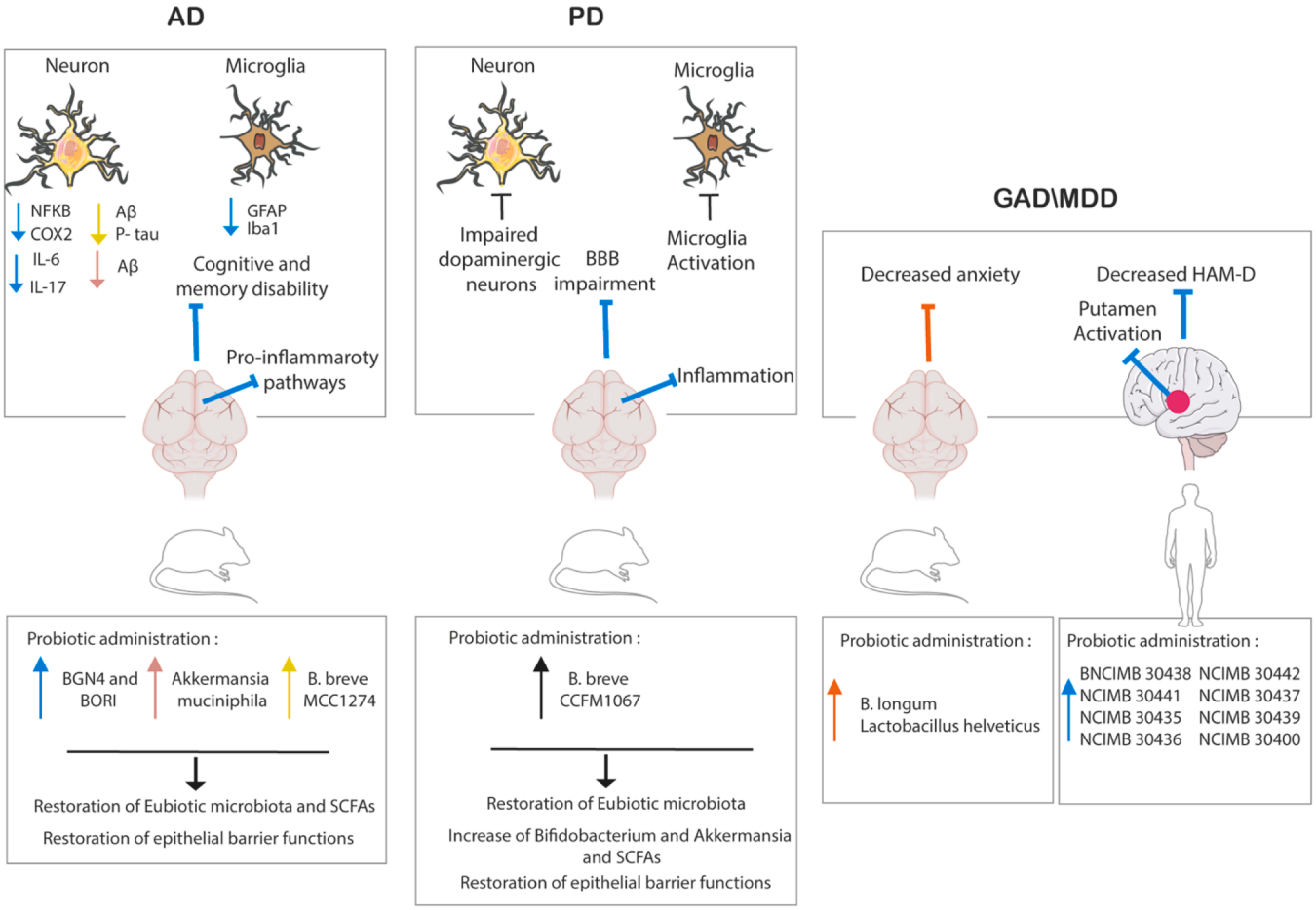

Fig. 3. Possible therapeutic strategy based on the administration of probiotics for neuro -degenerative and -psychiatric disorders. The administration of probiotics leads to the restoration of epithelial barrier function in the gut of AD and PD mice. (AD) The administration of *B. bifidum BNG4* and *B. longum BORI* downregulates the pro-inflammatory signaling in neurons and decreases the expression of GFAP and Iba1 in microglial cells. The intestinal colonization of probiotics causes also the expansion of *Akkermansia* which in turn reduces the amyloidosis. The administration of *B. breve* MCC1274 cause a reduction of the protein presenilin1, Aβ42 and the phosphorylated form of tau (P-tau). (PD) In PD mice the probiotic *B. breve* CCFM1067 restored microbial homeostasis, inducing the expansion of anti-inflammatory bacteria involved in the production of SCFAs and led to the preservation of BBB, dopaminergic neurons and microglia. **(MDD/GAD)** The administration of *B. longum* and *Lactobacillus helveticus* decreased the anxiety in preclinical mice model. The administration of a mix of different strains of *Bifidobacterium*, *Lactobacillus* and *Streptococcus* reduced the activation of Putamen and decreased HAM-D phenotype in patients.

prevent AD. Similarly, the Mediterranean diet which includes vegetables, fruits, nuts, whole grains, and healthy fats, fish, beans, and eggs could prevent and ameliorate PD, depression and anxiety [103,104,105].

On the opposite, several nutrients such as high-fat products, red and processed meat, elevated calories, salt, saturated fat, refined sugars, and low fatty acids characterizing the Western diet, have been found to worsen symptom severity of AD, PD and depression by contributing to gut-microbial-brain axis dysfunction and systemic inflammation [14,100,101,106]. The Mediterranean diet is divergent from the Western diet mainly for the amount of fiber intake. Fibers can be used as energy source by SCFA-producing bacteria. Consistently, the Mediterranean diet-associated microbiome is characterized by a high relative abundance of bacteria that can use fibers as energy source such as anti-inflammatory fiber-fermenting and SCFA-producing bacteria [104,107,108].

Besides these dietary regimens, specific food molecules seem to help these different pathologies.

Preclinical evidence on the APP mouse model of AD, showed that feeding for two weeks with Korean red ginseng (KRG) improved cognitive deficit, and reduced Aβ accumulation, microglial activation and BBB permeability. Correlative analyses based on 16SrRNA sequencing showed a significant expansion of *Lactobacillus* species upon KRG treatment, indicating that KRG bioactive molecules can increase the presence of anti-inflammatory bacterial species [109].

In aluminum trichloride and D-galactose induced AD mice, authors showed that crocin, a carotenoid isolated from saffron (Crocus sativus L.), enhanced memory and cognition capabilities, reduced cerebral content of Aβ1–42, rose the levels of glutathione peroxidase, superoxide dismutase, acetylcholine and choline acetyltransferase, and diminished circulating and cerebral ROS concentrations [110]. Moreover, the addition of crocin to the diet in FAD AD model, improved tightness and function of BBB, decreased toxic Aβ aggregates and upregulated the enzymes involved in their clearance (NEP, ABCA1) [111].

Another bioactive molecule able to inhibit AD progression is a species of ginger native to East Asia, the Alpinia oxyphylla Miquel (AOM) that can reduce the formation of Aβ and phosphorylation of tau, improving antioxidant, anti-inflammatory and anti-apoptosis effects, and preventing the activity of acetylcholinesterase [112]. Moreover, AOM mitigated neuroinflammation, Aβ deposition and phosphorylated-tau in LPS-induced learning and memory impairment [113] (Fig. 1).

Bioactive molecules derived from diet, seem to ameliorate and contrast also MDD/GAD symptoms. Jun S Lai and colleagues performed an association study between antioxidants and fatty acids with depression [105]. The study showed that omega 3 and other polyunsaturated

fatty acids had protective effects on depression in men and this was evident through the decrease of circulating C-reactive protein (CRP). By contrast, flavonoids had a greater impact in protecting women from depression. Bioactive molecules contained within plant species seemed to have an impact in the treatment of depression. In particular, plants from the genera Hemerocallis and Gladiolus showed different bioactive molecules including alkaloids, amino acids, anthocyanidins, carotenoids, flavonoids, glycoside, phenolic acids, phenylpropanoids, terpenes, and vitamins involved in antidepressant effects [114] (Fig. 3).

A particular class of bioactive molecules widely distributed in various plant sources is represented by polyphenols, a class of compounds that contain multiple phenolic structures and are characterized by the presence of one or more hydroxyl (-OH) groups attached to the aromatic rings. This heterogeneous class of molecules including resveratrol, and curcumin, possess antioxidant and anti-inflammatory properties, and cardiovascular protective effects and are recently described as promising candidates in protecting against neurodegenerative disorders like AD and PD, as well as mental health conditions like MDD and GAD. In AD resveratrol, found in grapes and berries, has an anti-amyloidogenic effect tested in various cell lines including the amyloid precursor isoform-containing 695 cell line (APP695), by facilitating the intracellular degradation of Aβ, through the modulation of the proteasome pathway [115]. A preclinical study confirmed the potential effect of resveratrol treatment with Res-selenium-peptide nanocomposites (TGN-Res@SeNPs), created by decorating functional selenium nanoparticles (Res@SeNPs) with a blood-brain barrier transport peptide (TGN peptide). When administered orally the TGN-Res@SeNPs exhibit cognitive improvement in AD by reducing amyloid-beta aggregation, decreasing oxidative stress, mitigating neuroinflammation, and positively modulating gut microbiota [116].

Moreover, in another clinical trial the group of AD patients treated for 52-weeks with resveratrol showed a significant reduction in Matrix Metalloproteinase-9 (MMP9) and Aβ42 levels in CSF, and a modulation of neuro-inflammation and immunity with the increase of macrophage-derived chemokine (MDC), interleukin-4 (IL-4), and fibroblast growth factor-2 (FGF-2). The alteration of molecular markers was associated also to an attenuated decline in mini-mental status examination (MMSE) and activities of daily living (ADL) scores [117]. Also in PD, resveratrol exhibited neuroprotective effects by reducing oxidative stress, neuroinflammation, and alpha-synuclein aggregation, ultimately preserving dopaminergic neurons [118,119]. Resveratrol has been studied also for its potential antidepressant and anxiolytic effects. It exerts its actions by modulating neurotransmitter activity, including serotonin and dopamine, exhibits antioxidant and anti-inflammatory properties, and enhance neuroplasticity [120].

Curcumin, a natural compound found in turmeric, has demonstrated promising effects in reducing the formation of amyloid-beta plaques while also exerting anti-inflammatory and antioxidant effects, thus preventing and treating AD [121]. In individuals with PD, curcumin has shown neuroprotective effects, and reduction of tau protein aggregation, that may aid in reducing neurodegeneration and inflammation. These effects are thought to be due to the activation of certain signaling pathways, specifically the BDNF (brain-derived neurotrophic factor) and PI3k/Akt pathways, which play roles in nerve regeneration and preventing cell death (apoptosis) [122]. Moreover, curcumin has been studied for its antidepressant effects in MDD as it modulates neurotransmitter levels, exhibits anti-inflammatory properties, influence neuroplasticity, hypothalamic-pituitary-adrenal disturbances, insulin resistance, oxidative and nitrosative stress, as well as the endocannabinoid system [123].

The described bioactive molecules seem to prevent and ameliorate the pathophysiology of neuro -degenerative -psychiatric disorders by inhibiting the pro-inflammatory triggers, decreasing the pathophysiology as the accumulation of Aβ42 and alpha-synuclein and preventing the maintenance of vasculature structures. However more studies are needed to understand molecular and metabolic mechanisms responsible for the observed effects, understanding how the combination of these substances could be useful in the reestablishment of gut-microbial-brain anti-inflammatory homeostasis. These findings should be then translated into human studies.

4.3. The effect of drugs on microbiota-gut-vascular-brain axis

There is evidence that AD, PD, MDD and GAD patients may have an altered gut microbiome, however given the occurrence of digestive side effects it raises the question if the medications affect or act through the gastrointestinal system and its microbial composition. Among the medications for the treatment of AD approved by the Food and Drug Administration (FDA) donepezil, rivastigmine, and galantamine are categorized as acetylcholinesterase inhibitors. Cholinesterase inhibitors, such as donepezil, can blocks the action of the acetylcholinesterase, increasing the levels of acetylcholine, a neurotransmitter involved in memory and cognitive processes in the brain. This drug can help slow down the decline in cognitive abilities improving memory and attention.

Investigations on the impact of Aβ and donepezil treatment on the fecal microbial community and brain metabolites in mice, showed an increased abundance of *Verrucomicrobia* and significant differences in the relative abundance of several taxa, including *Blautia* and *Akkermansia* [124]. Fecal analysis revealed elevated levels of oxalate, glycerol, xylose, and palmitoleate in the Aβ + donepezil group, while brain tissue analysis showed elevated levels of oxalate, pyroglutamic acid, hypoxanthine, and inosine compared to the Aβ group. This study points out the possibility that the donepezil could modify the microbiota which in turn could be involved in the modulation of metabolic composition. The potential association between gut microbiota and treatment efficacy was demonstrated by the combination of donepezil with *Lactobacillus plantarum* C29 and C29-fermented soybean DW2009 which showed stronger effects in mitigating cognitive impairment-like behaviors and suppressing neuroinflammation compared to individual treatments [125].

Sodium oligomannate (GV-971), recently approved for the first time by the FDA, is an orally administered mixture of acidic linear oligosaccharides developed for the treatment of AD. This new treatment, used to improve cognitive function of mild to moderate AD, was shown to remodel the gut microbiota by reducing specific metabolite concentrations and neuroinflammation in the brain [126,127]. Overall, these studies highlight the potential role of AD drugs, including GV-971 and donepezil, in modulating the gut microbiota and the gut-brain axis.

In PD there is some evidence regarding the importance of gut-brain-microbiota axis in mediating drug efficacy. Levodopa, also known as L-dopa, is a medication commonly used in the treatment of PD. It is a precursor of dopamine and is converted in the brain, where it helps to replenish the depleted dopamine levels characteristic of PD. By increasing dopamine levels, levodopa helps alleviate the motor symptoms associated with the condition, such as tremors, rigidity, and bradykinesia. Levodopa is often combined with other medications, such as carbidopa, a peripheral metabolism-blocking drugs, to avoid the conversion outside the brain and enhance its effectiveness. However, L-dopa can also undergo decarboxylation in the gastrointestinal tract, which poses challenges as dopamine produced in the periphery cannot cross the blood-brain barrier and leads to undesirable side effects. The gut microbiota has the ability to metabolize the medication levodopa (L-dopa) used in the treatment of Parkinson's disease. In particular, recent research has uncovered an interspecies pathway in which gut bacteria metabolize L-dopa. This pathway involves the conversion of L-dopa to dopamine by a tyrosine decarboxylase enzyme found in *Enterococcus faecalis*, followed by the transformation of dopamine to m-tyramine by a dehydroxylase enzyme from *Eggerthella lenta* [128]. Microbial metabolism can significantly decrease drug availability and potentially induce side effects. On the other hand, the microbial-dependent pathway involving phenylalanine-tyrosine-dopamine may play a pivotal role in supplying dopamine to the brain. The rate-limiting

enzyme, tyrosine hydroxylase (TH), is responsible for catalyzing the hydroxylation of tyrosine, resulting in the production of L-dopa with the assistance of tetrahydrobiopterin (BH4) as a coenzyme. Recent research has proposed that oral berberine (BBR) holds promise in enhancing this pathway by promoting BH4 production, thereby augmenting TH activity and expediting L-dopa synthesis by gut bacteria. The L-dopa generated by intestinal bacteria enters the brain through circulation and subsequently undergoes conversion to dopamine. To investigate the communication between the gut and the brain activated by BBR, experiments involving the transplantation of *Enterococcus faecalis* or *Enterococcus faecium* bacteria into PD mice demonstrated a significant elevation in brain dopamine levels and notable improvements in PD symptoms [129].

These results where additionally confirmed through the treatment of 28 patients with hyperlipidemia with BBR: the treatment lead to the expansion of *Enterococcus faecalis* and *faecium* as well as of blood and fecal L-dopa levels. Patients suffering from major depressive disorder (MDD) display a distinct gut microbiome that experiences alterations subsequent to the administration of Serotonin Reuptake Inhibitors (SSRIs) [130]. Interestingly a study showed that the dysbiotic gut microbiota of MDD patients tends to return to the homeostasis. Moreover, correlative analysis between bacterial species and SSRI efficiency revealed that *Blautia*, *Bifidobacterium*, and *Coprococcus*, which exhibited higher relative abundance in the group with treatment effectiveness, were associated with the efficacy of SSRIs antidepressants [131]. Overall, the current evidence suggests that medications used for AD, PD and MDD treatment can have effects on the gut microbiota, and in turn, the microbiota could impact the effectiveness of treatments.

5. Conclusions and perspectives

In this review we summarized recent data on bacterial molecular pathways and metabolites that are functionally associated with the development or protection of neurodegenerative diseases such as AD, PD and major depressive and anxiety disorders. Functional studies are helping to unravel the role of the two major components of the microbiota, i.e., pro- and anti- inflammatory microbes, in the gut-brain-axis. A crucial point seems to be the strict correlation between microbial dysbiosis, mucosal immunity and intestinal vascular impairment which in turn could trigger the low-grade release of systemic inflammatory mediators and bacterial components such as LPS thus initiating or boosting the development of neurological disorders. The data reported here strongly suggest that microbial and systemic inflammatory molecules could induce cerebral vascular impairment, microglia activation, neuronal malfunctioning and pre-post synaptic unbalance. This evidence, combined to early clinical intestinal manifestation in AD, PD, MD and GAD patients and the high risk of IBD or IBS patients to develop neurodegenerative disorders, supports a role for a dysbiotic microbiome and loss of mucosal homeostasis, in triggering chronic peripheral inflammation and driving neuro-inflammation and -degeneration.

Several reports highlight the central role of vascular barriers which control gut and brain permeability in the development of neurological disorders. In particular, the choroid plexus vascular barrier is taking the stage in anxiety disorders. We recently demonstrated that the genetic closure of the PVB in a preclinical mouse model, led to the anxiety-like behavior even in the absence of inflammation, because of brain isolation [14]. Hence, behavioral defects can be the result of an isolation of the brain from the rest of the body and may be the payload to avoid propagation of inflammation to the brain. On the contrary, we do not know what happens when this defense mechanism is lost, maybe due to continuous propagation of inflammation. Is this contributing to neuroinflammation? Testing if the PVB could be compromised in preclinical models of neurodegenerative disorders and understanding the timing and triggering factors involved in its closure could be fundamental in the comprehension of multifactorial disorders. The longitudinal analysis of PVB accessibility in mice and patients at different ages could be important to study if aging could lead to vascular impairment of the barrier losing the required filter of the metabolic output delivered by the gut. It will be interesting to evaluate the effect of the loss of PVB barrier properties, the comparison with BBB functionality, and their effect on the CNS protection programs. Thus, more studies on the relationship between the role of bacteria, and their products, in the prevention and driving of GVB, BBB and PVB loss of function are needed.

The possibility of using microbiota-based therapies, although promising, remains to be confirmed through human intervention studies. The restoration of protective microbial taxa reconstituting the intestinal barrier integrity and restoring the presence of anti-inflammatory signals such as butyrate could be involved in controlling intestinal barrier integrity and inflammation across the gut-brain axis.

Other bioactive molecules which could affect neuroendocrine, immune, epigenetic, and molecular mechanisms involved in microglial activation, synaptic dysfunction, plasticity and neurogenesis are under intense investigation. These bioactive molecules, which include microbial metabolites, Phyto and diet molecules, could also preserve microbial diversity, protecting the anti-inflammatory core of bacteria. As most of the beneficial activities of the microbiota are associated to their metabolic products, also called postbiotics [132,133], understanding their functional role as individual molecules will help identify personalized nutritional intervention for patients with neurological disorders. New studies will help define the action of these molecules and their possible use as new preventive or therapeutic tools.

Declaration

The authors declare no competing financial interests.

Acknowledgements

These researchers are supported by AIRC 5x1000 2018 ID.21147 and PRIN (Ministero dell'Istruzione dell'Università e della Ricerca) grant no. 2017J3E2W2, PNRR, to Maria Rescigno.

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