EXTRA Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2018;8:360–381
DOI: 10.1159/000492491
Received: May 4, 2018
Accepted: July 26, 2018
Published online: October 18, 2018

Review Article

Current Perspectives and Mechanisms of Relationship between Intestinal Microbiota Dysfunction and Dementia: A Review

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Keywords

Dementia · Intestinal microbiota · Dysbiome repertoire · Gut-brain axis · Microbiota-brain axis

Abstract

Background: Accumulating data suggest a crucial role of the intestinal microbiota in the development and progression of neurodegenerative diseases. More recently, emerging reports have revealed an association between intestinal microbiota dysfunctions and dementia, a debilitating multifactorial disorder, characterized by progressive deterioration of cognition and behavior that interferes with the social and professional life of the sufferer. However, the mechanisms of this association are not fully understood. ***Summary:*** In this review, I discuss recent data that suggest mechanisms of cross-talk between intestinal microbiota dysfunction and the brain that underlie the development of dementia. Potential therapeutic options for dementia are also discussed. The pleiotropic signaling of the metabolic products of the intestinal microbiota together with their specific roles in the maintenance of both the intestinal and blood-brain barriers as well as regulation of local, distant, and circulating immunocytes, and enteric, visceral, and central neural functions are integral to a healthy gut and brain. ***Key Messages:*** Research investigating the effect of intestinal microbiota dysfunctions on brain health should focus on multiple interrelated systems involving local and central neuroendocrine, immunocyte, and neural signaling of microbial products and transmitters and neurohumoral cells that not only maintain intestinal, but also blood brain-barrier integrity. The change in intestinal microbiome/dysbiome repertoire is crucial to the development of dementia.

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DOI: 10.1159/000492491

Introduction

The intestinal or gut microbiota can be defined as the overall species of beneficial microbes that inhabit the gastrointestinal tract. The estimated number of these microbes is ~10^{14} comprising ~1,000 species, mainly anaerobic bacteria and archaea, with a fewer number of protozoa, fungi, and other microbes, inhabiting every region of the gut. The gut microbiota represents over 90% of the total microbes that colonize the human body [1, 2].

The intestinal microbes of any region of the gut can substantially influence the health state and development or progression of diseases [3–5]. These microbes regulate homeostasis and metabolism, in part, through their beneficial activities on intestinal and distant histohematological barrier and permeability, immune system functions, gut motility, absorption of nutrients, and synthesis of microbial-derived beneficial bioactive molecules [6, 7]. Though the gut microbiota has a huge beneficial role, it can become potentially harmful, especially under unfavorable conditions of the intestinal microenvironment, possibly resulting from unhealthy diet and nutrition, antibiotic administration, or pathogenic invasion [8–10]. The harmful effects of the intestinal microbiota are due to its abnormal behavior, characterized by the presence of pathogenic microbes or a substantial reduction in the proportion of the intestinal beneficial microbes [1, 8].

Emerging data have implicated abnormal intestinal microbiota in the development of dementia [11, 12]. Interestingly, accumulating evidence indicates a key role of the intestinal microbiota in host metabolic regulation, inflammation, synthesis of a couple of molecules that mediate neurohumoral responses, and age-related changes associated with the intestinal microbiota, gut, and functionally related organs [13, 14].

Dementia is a devastating complex, multifactorial clinical syndrome, characterized by progressive deterioration of memory, attention, thinking, comprehension, language, and behavior, severe enough to interfere with occupational or social life, which leads to disability, and subsequently death of the individual [15–20]. The growing prevalence of dementia poses a serious public health concern worldwide [15, 16, 21, 22]. In 2003 worldwide prevalence of dementia was 27.7 million [15]. In 2013 the worldwide prevalence of dementia reached 44.4 million [23]. Two years later, precisely in 2015, the number of individuals suffering from dementia reached 46.8 million, indicating an increment of about 1 million per year in new cases. Recent statistics has revealed that the number of demented persons is expected to increase at an alarming rate, reaching 75.6 million by 2030 [23].

Dementia is associated with high financial burden to the caregiver, family, and healthcare system [17, 18, 24, 25]. Consequently, the increasing prevalence of dementia in the world will lead to enormous financial burden [23, 24]. In 2003 the worldwide costs for dementia was estimated at USD 156 billion [15]. In 2009 alone, the total worldwide cost of dementia increased to USD 422 billion [26]. It increased to USD 817.9 billion in 2010 [27]. By the end of 2018 it is expected to hit USD 1 trillion [27]. These data indicate an urgent need to step up measures that will identify at-risk individuals, and the necessity for increasing global coalescence for novel translational research on the multiple mechanisms of development of dementia that may lead to the potential discovery of newer frontiers in dementia treatment and identification of specific windows of interactions between certain disorders and the brain that underlie the development of dementia.

The constantly growing prevalence and burden of the disease indicate the necessity to investigate the complex mechanisms that underlie the development of dementia and search for newer avenues that could provide potential therapeutic options for the disease. In this paper, I review recent data that suggest mechanisms of cross-talk between intestinal micro-

biota dysfunctions and the brain that underlie the development of dementia. Contemporary issues about the intestinal microbiota-brain axis are also discussed. The paper also discusses potential therapeutic options for dementia prevention and development.

Current Perspectives on the Etiopathogenesis of Dementia

Brain Disorders and Infectious Diseases that Predispose to the Development of Dementia

Dementia is usually caused by neurodegenerative disorders such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease [7, 28–31]. Though Alzheimer's disease accounts for approximately 60–75% of all cases of dementia worldwide [7, 16, 32], the condition can also occur in up to 80% of Parkinson's disease patients [28] and about 40–65% of patients with multiple sclerosis [33, 34]. Dementia can result from cerebrovascular disease such as stroke (ischemic or hemorrhagic), certain infections such as Creutzfeldt-Jakob disease, herpes simplex virus type 1, human immunodeficiency virus, syphilis, borrelia, toxoplasmosis, cryptococcosis, cysticercosis, cytomegalovirus, *Helicobacter pylori, Chlamydophila pneumoniae, Borrelia burgdorferi,* Huntington's chorea, corticobasal syndrome, progressive supranuclear palsy, Niemann-Pick disease type C, normal pressure hydrocephalus, and prion diseases. Alcohol misuse can also cause dementia [7, 21, 28, 30, 35–38]. These brain disorders lead to inflammation or dysfunctions in neural or glial metabolism that eventually result in loss of connections, and eventually death of brain cells that characterize dementia [7, 21]. However, depending on the physiological reserve of the organism and induction of the compensatory mechanisms, cognitive impairment leading to dementia may be static, progressive, or reversible [30, 39, 40].

Advanced Glycation End Products due to Senescence as a Possible Cause of Dementia

Several reports have revealed that nonenzymatic glycosylation of proteins due to senescence form advanced glycation end products that are resistant to proteolytic processing and can induce protein cross-linking, resulting in induction of oxidative stress and free radical formation, and possibly formation and accumulation of β-amyloid, and inflammation as in the case of Alzheimer's progressive cognitive impairment or dementia [41–45]. The receptors for the harmful metabolites and proinflammatory molecules due to oxidative stress in neurons and glia (microglia and astrocytes) are believed to mediate the pathological processes observed in dementia [46]. These receptors include the following: NLRP1 (nucleotide-binding oligomerization domain-like receptor containing pyrin domain 1), NLRP2–5, NLRP9, and NLRP10; TREM2 (triggering receptor expressed on myeloid cells 2), SRA (scavenger receptor type A); scavenger receptor B-1 (SRB-1); MARCO (macrophage receptor with collagenous structure); RAGE (receptor for advanced-glycosylation end products) and the receptors of the complement system such as Fc receptors; FPR2 (formyl peptide receptor 2); CD11 (cluster of differentiation 11), CD21, CD33, CD35, CD36, CD45, CD68, CD88, and complement receptor 3a and 5a (CD88); TLR2 (toll-like receptor type 2), TLR3, TLR4, TLR6, and TLR7; CMKLR1 (chemokine-like receptor 1); CXCR5 (C-X-C motif chemokine receptor 5) and CXCR16; EP2 (prostaglandin E2 receptor subtype 2); FPR1 and FPRL1 (formyl peptide receptor type 1 and formyl peptide receptor like 1); and leukocyte immunoglobulin-like receptor B2 (LilrB2) among others [47–56]. All these receptors are known as pattern recognition receptors (PRRs) [57–59]. PRRs sense and recognize certain motifs on pathogens (pathogen-associated molecular patterns, PAMPs) or molecules released due to cellular damage (damage-associated molecular patterns, DAMPs) [60]. Examples of PAMPs include peptidoglycan, lipopolysaccharides, triacyl lipoproteins, zymosan, teichoic acid, lipoteichoic acid, lipoarabinomannan, arabinogalactan, lipopeptides, flagellin, and foreign nuclear mate-

rials such as bacterial DNA and viral RNA, which can trigger the production of proinflammatory cytokines that may trigger the onset of certain peripheral and central diseases characterized by inflammatory reactions [60]. Examples of DAMPs include certain extracellular matrix components released during cell damage (e.g., laminin, fibronectin, elastin, and collagen-derived peptides, matrix metalloproteinase-3 and -13, versican, and biglycan) and cytoplasmic proteins such as heat shock proteins (e.g., Hsp60), RNA and mitochondrial DNA, nuclear DNA, IL-1, high-mobility group box 1 protein, histones, adenosine triphosphate, and antimicrobial peptides – which are altogether known as "alarmins" [60–68]. The recognition of PAMPs or DAMPs by PRRs (e.g., TLRs, CD14) activates signaling pathways such as nuclear factor kappa of B cell (NF-κB) and inducible nitric oxide synthase (iNOS), leading to the synthesis of proinflammatory cytokines and interferons (IFN-γ), and tumor necrosis factor alpha (TNF-α), as well as the activation of a range of oxidative stress-related molecules including MAPK (mitogen-activated protein kinase), PI3K (phosphatidylinositol 3-kinase), PKC (protein kinase C), AP-1 (activator protein 1), p38, and numerous autophagy pathways [60, 62, 63, 69]. PAMPs signal downstream via the JAK-STAT (Janus kinase/signal transducers and activators of transcription) pathway to initiate the synthesis of interleukins and TNF-α [70]. This pathway of proinflammatory cytokine synthesis is termed the MyD88-dependent pathway because signaling through this pathway occurs via activation of the cytoplasmic adaptor protein myeloid differentiation primary response protein 88 (MyD88). However, there is also an MyD88-independent pathway that controls IFN-β synthesis and activity [60]. This "recognition signaling" occurs at the local (gut epithelium) and central level (brain). In reality, the host cell uses multiple pathways to recognize pathogenic microbes. For instance, the pattern recognition molecules MBL (mannose-binding lectin) and ficolins functioning as opsonins can form a linkage with MBL-associated serine protease-2 (MASP-2), resulting to the formation of MBL-MASP-2 complex, which can recognize and bind to certain carbohydrate motifs on the microbial cell wall to initiate a series of reactions that culminate in the production of proinflammatory cytokines. The signaling of these cytokines can result in altered balance or composition of the intestinal microbes, and as a consequence, increased intestinal permeability [60, 71–73]. The proinflammatory cytokines can be transported to different tissues including the brain, initiating a neuroinflammatory process in the blood-brain barrier that decreases its permeability [60, 74, 75]. These processes and the signaling cascades mediated by the activation of the amyloid peptide receptors also interact with a range of neurotransmitter systems, which add to the deterioration of cognitive functions [76–78].

A Possible Role of the Siderocalin-Brain-Type Organic Cation Transporter 1-Megalin Complex, Mediating Neuroinflammation, in the Development of Dementia

The recent discovery of the ubiquitous lipocalin-2 (also known as siderocalin) and its purported role in the brain has sparked considerable interest in the behavior and signaling pathway mediated by this secreted glycoprotein. Though information about the peptide is scanty, functional lipocalin-2 forms a complex with brain-type organic cation transporter 1 and megalin (also known as low-density lipoprotein-related protein 2, LRP2) and contributes to the transport of small hydrophobic molecules. Interestingly the microglial, astroglial, epithelial, and neuronal type of this complex has been shown to be involved in neuroinflammation [79–81]. Furthermore, LRP2, a receptor for β-amyloid protein, has been implicated in late-onset Alzheimer's disease. In addition to LRP2, LRP1 can form complexes with apolipoprotein E to mediate clearance of β-amyloid protein across the blood-brain barrier. Pharmacological agents that will affect the activities of LRP1 are currently considered potential therapeutic options for the treatment of Alzheimer's disease [82–84].

Inorganic Deposits in the Brain as a Possible Cause of Dementia

Inorganic deposits in the brain can initiate free radical processes that result in lipid peroxidation, protein oxidation, formation of reactive oxygen species, and subsequently accumulation of calcium ion that results to excitatory toxicity [85]. These processes underlie oxidative stress, which activates microglia, at least in part, by stimulating PRRs (e.g., TLRs), resulting in phagocytosis of the toxic molecules. The result of these processes may lead to neurodegeneration [86–88]. Previous studies showed that murine microglial cells exposed in vitro to aluminosilicate particles stimulated the generation of free radical reactive oxygen metabolites such as hydrogen peroxide, superoxide, and hydroxyl free radicals, leading to tissue injury [89, 90]. Indeed, human studies of Alzheimer's disease have confirmed deposits of inorganic metals in amyloid deposits in specific brain regions [91–93].

Toxic metals activate signaling pathways related to redox transcription factors such as NF-κB, AP-1, MTF-1 (metal-responsive transcription factor 1), p53 (53-kilodalton tumor protein), ethylene responsive transcription factor 1 (ERF1), ERF2, Ref-1 (redox factor 1), extracellular-signal-regulated kinases (ERK1/2), and c-Jun NH 2-terminal kinase (JNK) [94–99]. Indeed. some deposits that characterize senile dementia have been observed to contain inorganic aluminosilicate particles [90]. Interestingly, amyloid deposits that characterize Alzheimer's dementia or progressive cognitive impairment were shown to result in lipid peroxidation and protein phosphorylation, altering glucose metabolism and the mTOR signaling pathway, leading to neuronal death [100].

Toxigenic Metabolites and Dementia

Toxic products of cellular metabolism can also cause neuroinflammation or brain tissue or vascular injury that subsequently leads to demyelination and neurodegeneration [87, 88, 90, 101, 102]. Indeed, dementia due to vascular dysfunction accounts for about 15–30% of all dementia cases [30]. A ^{1}H-MRS study by Herminghaus et al. [103] (2003) found that concentration of certain metabolites, in particular *N*-acetyl aspartate, was decreased, while total creatine and *myo*-inositol were significantly increased in the brain of Alzheimer's disease patients. However, comorbid factors may be responsible for the association between metabolic dysfunctions and cognitive impairment [104]. This association has been reviewed elsewhere [105].

Alteration in the Composition of Beneficial Intestinal Microbiota as a Possible Cause of Dementia

A couple of studies have shown alterations in the intestinal microbiota in dementia [7, 9–12]. A substantial decrease in intestinal microbes, especially *Lactobacillus and Bifidobacterium*, as well as changes in *Coprobacillus*, *Dorea*, *Enterococcaceae*, *Staphylococcus*, *Faecalibacterium*, *Coprococcus*, and *Roseburia*, are believed to be responsible for cognitive impairment and cerebral hypometabolism in neurodegeneration that characterize dementia [106]. The essential role of the intestinal microbiota in regulating both local and distant tissues such as the blood-brain barrier is mediated via multiple mechanisms, which are discussed below [6, 7, 13, 14].

Functional Communication Pathways between the Intestinal Microbiota and the Brain

The connection between the gut and the brain has been suggested since antiquity when the Greek philosophers and scientists suggested a possible relationship between gut disorders and epilepsy [1, 2]. In fact, Hippocrates around 400 B.C. even quoted that "death sits in the

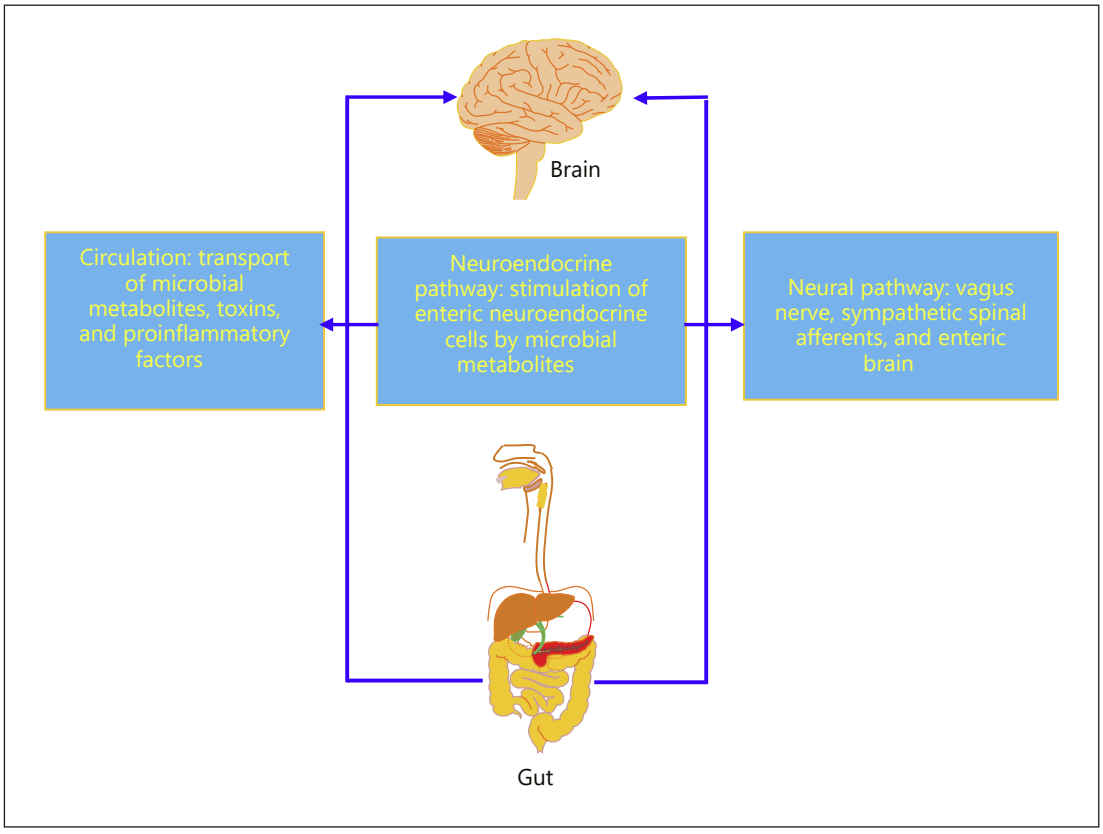


Fig. 1. Pathways of gut microbiota-brain cross-talk.

bowels," possibly referring to the disorders associated with bowel malfunctioning [107]. It should be noted, however, that the gut microbiota-dementia connection represents only a portion of the gut-brain axis. The functional pathways through which the intestinal microbiota communicate with the brain, also known as intestinal microbiota-brain cross-talk, is a bidirectional functional communication network between the microbes and the brain that comprises neuroendocrine, neural, and neuroimmune signaling pathways (Fig. 1). The endocrine pathway is mediated by the interaction between the intestinal microbiota and neuroendocrine cells of the gut. The neural pathway of intestinal microbiota-brain cross-talk occurs through the interaction of the intestinal microbiota with the central nervous system (including the hypothalamic-pituitary-adrenal axis, HPA axis), the autonomic nervous system (via the vagus nerve and the sympathetic nerve fibers), and the enteric nervous system. The immune pathway that mediates the cross-talk occurs through the interaction between the intestinal microbiota and immune molecules [108–110].

The metabolites of the intestinal microbiota such as short-chain fatty acids, GABA (γ-amino butyric acid), serotonin, norepinephrine, histamine, etc. regulate a range of physiological processes in the gut and distant organs, including the brain, via their interaction with neural, neuroendocrine, and immune signaling pathways [108, 110–114].

Intestinal Microbiota-Neural Signaling

In recent papers, I noted that the gut alone synthesizes over sixty types of transmitter molecules that not only influence gut functions, but also nervous system activity [115, 116].

Thus, dysfunctions in the gut homeostasis due to dysfunction in intestinal microbiota can result in disorder in the synthesis of the gut neurotransmitters, neuropeptides, hormones, and immunomodulators, which can affect the gut-brain axis [60]. Some of the gut-derived hormones can affect the functions and composition of the intestinal microbiota. Surprisingly, not only the gut cells synthesize these neurotransmitters, neuropeptides, hormones, and immunomodulators, but also the intestinal microbiota. Furthermore, the gut microbiota can trigger the synthesis of these molecules from epithelial neuroendocrine cells of the gut. So, the cholinogenic gut microbe, *Lactobacillus* sp., produces acetylcholine that affects vagal, neuroendocrine, and neuroimmune signaling. *Bacillus* sp. is a dopaminergic microbe [7, 115, 116]. The intestinal microbiota regulates the HPA axis by the release of cortisol, which may affect microglia activation and cytokine release, homing of distant and local immunocytes to the site of cerebral aggression. The intestinal microbiota can affect long-term potentiation (LTP) via its interaction and regulation of GABA, N-methyl-D-aspartate (NMDA) receptor, postsynaptic density marker 95 (PSD-95), and brain-derived neurotrophic factor (BDNF) [117, 118]. LTP is an important phenomenon in higher mental functions, memory formation, and cognitive processes in which activity-dependent processes are persistently enhanced at neuronal synapses [119, 120]. Dysfunction in LTP induction has been implicated in a range of cognitive impairments that accompany ageing including Alzheimer's disease and dementia [120, 121].

Intestinal Microbiota-Endocrine Signaling

A couple of endocrine factors released by the intestinal microbiota or secreted by the endocrine cells of the gut under the action of the intestinal microbiota can be transported via the circulatory system to the brain where they trigger a range of signaling pathways responsible for higher mental functioning [6, 115]. On the other hand, substances released by the brain can also affect the activities of the gut and intestinal microbiota [6]. Thus, the endocrine pathway represents a crucial bidirectional link between the gut microbiota and brain structures that allows the transfer of humoral factors, which mediate a range of brain activities including cognition [122, 123]. Gut-derived hormones regulate energy homeostasis and exert a substantial influence on the gut's little brain and central nervous system, thereby modulating cognitive functions [1, 60, 75].

Intestinal microbiota dysfunctions result in alteration in microbe- and gut-synthesized hormones including neurotrophic factors and their receptor systems [124, 125], which may predispose to the development of neuronal and glial cell death. Growth hormones protect neurons from toxicity and excessive excitatory signaling [126], in part by stabilizing Ca^{2+} signaling, stabilizing the expression and NMDA and GABA receptor-mediated signaling [115, 116, 126]. In addition, adequate humoral signaling exerts protective effects on the mitochondria. This way, growth factors prevent neurodegenerative processes that result in dementia [75]. Furthermore, the gut-synthesized hormones leptin, ghrelin, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide confer neuroprotective effects against neurotoxicity induced by harmful pathogenic microbial toxins (toxigenic metabolites) [126–128]. Consequently, application of analogs of these hormones can be helpful in the treatment of cases of dementia.

Intestinal Microbiota Signaling Is Coupled to Second Messenger Generation: Cooperativity or Confluence of Neural and Endocrine Signaling Pathways?

Ca^{2+} is a second messenger that links several signaling pathways in the cell. This cellular ion is required to maintain ongoing physiological processes. However, prolonged or excessive increase can become detrimental to the cell [115, 116, 129, 130]. Importantly, destabilization of Ca^{2+} signaling has been implicated in neurodegeneration [126, 131, 132]. Dysfunctional

Ca^{2+} signaling due to alteration in intestinal microbiota can occur both in the gut and brain. Disorder in intestinal microbiota can result in accumulation of Ca^{2+} ions, which can lead to cellular toxicity. Although the mechanisms are not fully understood, it may involve multiple disorders involving functional protein complexes (e.g., claudins, occludins, and zonula adherens) which increase paracellular shunt activity in the gut epithelium. This may lead to excessive excitation of the extracellular G-protein-coupled Ca^{2+} sensing receptor (CaSR) located on different cells of the gut including neuroendocrine and vagal nerve endings [115, 116, 130, 133–135].

Activation of this receptor can occur not only by extracellular Ca^{2+}, but also other molecules including Mg^{2+}, amino acids, polyamines, and drugs (CaSR agonists or calcimimetics and calcilytics or CaSR antagonists) [136, 137]. But there may be a bidirectional relationship between the CaSR and the intestinal microbiota. A relatively recent report revealed that deficiency of this receptor resulted to intestinal microbiota dysfunction, in addition to reduced intestinal barrier and disordered immune response. This suggests that CaSR may serve as a therapeutic target in dysfunctions of the intestinal microbiota [138].

The vagus nerve endings that mediate signal transfer in the microbiota-gut-brain axis express the CaSR. Consequently, dysfunctions of CaSR signaling in the vagus nerve have been associated with disorder in neurotransmission associated with this nerve and its integrating center with excitatory and inhibitory outputs to multiple brain regions [115, 116, 130, 133, 135]. Moreover, accumulation of Ca^{2+} in the cytosol of both neurons and glial cells can activate proteases and lipases, which degrade plasma membrane proteins and lipid molecules to generate free radicals that further cause destruction of cellular components. Accumulation of cytosolic Ca^{2+} can also activate Ca^{2+}-dependent proteases, resulting in hyperphosphorylation of microtubule proteins, triggering changes in the cytoskeleton, similar to those observed in dementia [115, 116, 130–132].

Dementia-Dysbiome Repertoire

Sudo et al. [139] were the first to report a link between the gut microbiota and the brain. They reported stress response mediated by the HPA axis and decreased BDNF levels in the hippocampus of germ-free mice. Since then, there has been increased interest in studying the functional connectivity between the brain and intestinal microbiota in normal and pathological cells [6, 140]. Recent studies have shown that intestinal microbiota dysfunctions may underlie the development of progressive cognitive impairment or dementia [10–12]. A recent analysis identified a strong association between dementia and dysbiosis of the intestinal microbiota or dysbiome – the total population of harmful microbes that predisposes to the development of dementia [12]. The number of *Clostridium difficile* in patients with dementia was substantially increased compared to controls [12].

The intestinal microbe *Cyanobacteria*, occurring during gut dys-homeostasis, can synthesize neurotoxins such as saxitoxin, α-anatoxin, and β-*N*-methylamino-L-alanine, which may contribute to the development of dementia [7]. Some gut microbes including *Citrobacter*, *Escherichia coli, Klebsiella*, *Mycobacteria*, *Pseudomonas, Streptococcus*, *Streptomyces, Staphylococcus, Salmonella*, and *Bacillus* species among others are capable of synthesizing amyloid peptides (e.g., curli amyloid fibers, $A\beta_{42}$, having CsgA as the major subunits, but also containing CsgB) that are transported and deposited in the brain and may potentially cause cognitive impairment or dementia [7, 72, 141–143]. By a mechanism of molecular mimicry, these bacterial amyloids can cause neuroinflammation and subsequently neurodegeneration by interfering with inflammatory pathways mediated by TLR2 and NF-κB signaling [144]. The bacterial amyloids also exert local effects on the gut by destroying the protective defenses of

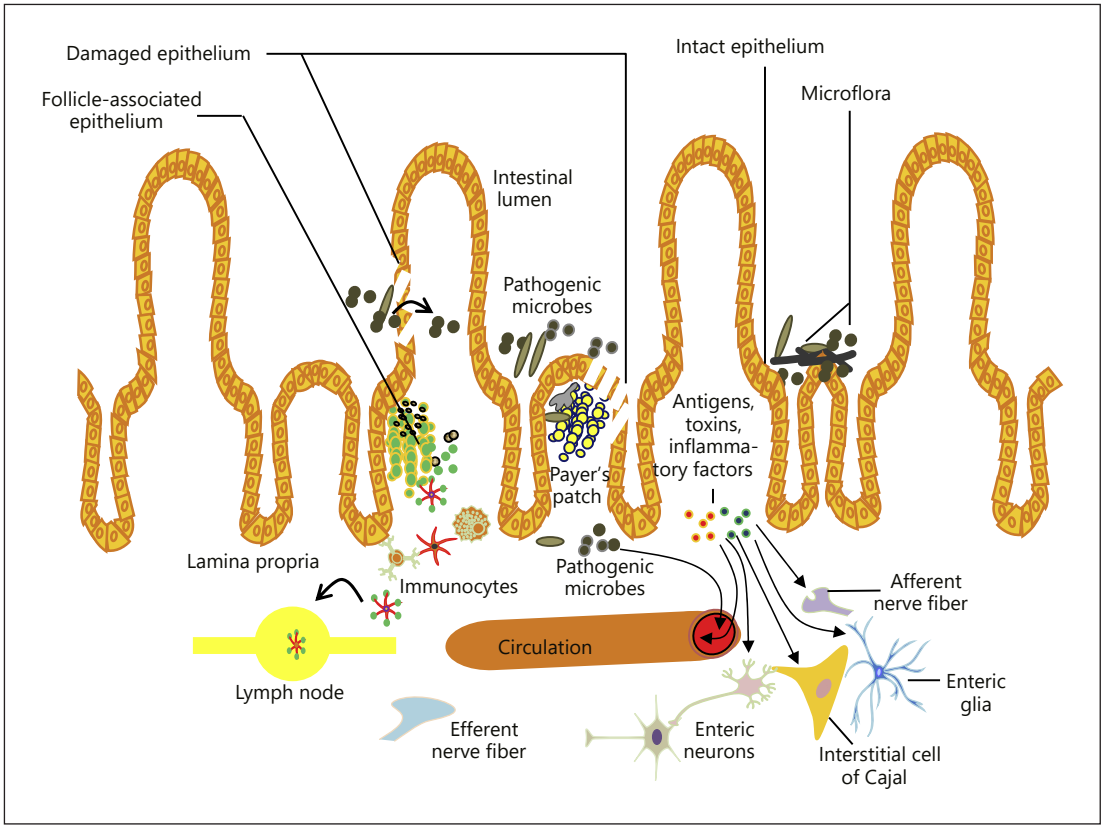


Fig. 2. The gut mucosa showing intact epithelium and defective epithelium resulting from pathogenic microbial activity, which causes disorder in the sentinel system of the gut (mucous membrane, follicle-associated epithelium, Peyer patches, lymph nodes, resident immunocytes). The defect enhances translocation of pathogenic microbes and toxigenic metabolites, as well as proinflammatory factors, to different regions of the gut where they trigger local inflammatory response, activating immunocytes. The pathogenic microbes and toxigenic metabolites, as well as proinflammatory and inflammatory factors, released from the site of defect and during local inflammatory responses can be transported via circulation to the brain [1, 112]. Furthermore, the toxic metabolites and other substances released can stimulate the enteric brain comprising the enteric glia, the enteric neurons, and the interstitial cells of Cajal, and also regulate the activity and synthesis machinery of neuroendocrine cells and afferent fibers of the vagus and spinal nerves. The lymphatic vessels are also implicated in the inflammatory responses [1].

the host, at least in part, through enhancement of surface adhesion of pathogenic microbes and biofilm development [7, 141–143].

A decrease in the number of *Bifidobacteria*, including *B. fragilis,* and *Eubacterium rectale* correlates with cerebrospinal fluid biomarkers of Alzheimer's disease [145, 146]. The results of these studies raise important questions as to whether or not some microbes are responsible for the development of dementia. Causative agents of neurodegeneration are yet to be identified [147]. There is currently no effective treatment for dementia as conventional strategies identify patients very late and the treatment usually addresses the symptoms and not the underlying causes [7, 101]. As a result, the prevalence of dementia continues to increase worldwide [148]. In all neurodegenerative diseases associated with dementia there is a reported difference in the composition of gut microbiota compared to that in healthy individuals [7, 146, 147]. Moreover, age-related changes in the composition of the gut microbiota are also associated with dementia [11, 149].

The gut microbiota is responsible for modulating several gut hormones and peptides, including cholecystokinin, corticotropin-releasing factor, neuropeptide Y, peptide YY, pancreatic polypeptide, serotonin, glucagon-like peptide, and ghrelin, which through the vagal and spinal afferents, neuroendocrine and immunocyte signaling can exert a considerable impact on brain functions [140, 150]. Furthermore, the intestinal microbiota has been shown to control the metabolic pathways of synthesis of certain neurotransmitters. The intestinal microbiota regulates the kynurenine pathway involved in tryptophan metabolism, which is required for the synthesis of serotonin [108].

Dysfunctional Intestinal Microbiota Is Associated with Disordered Intestinal and Blood-Brain Barriers: Decrease in Beneficial Intestinal Bacteria and Increase in Potentially Harmful Ones Enhances the Development of Dementia

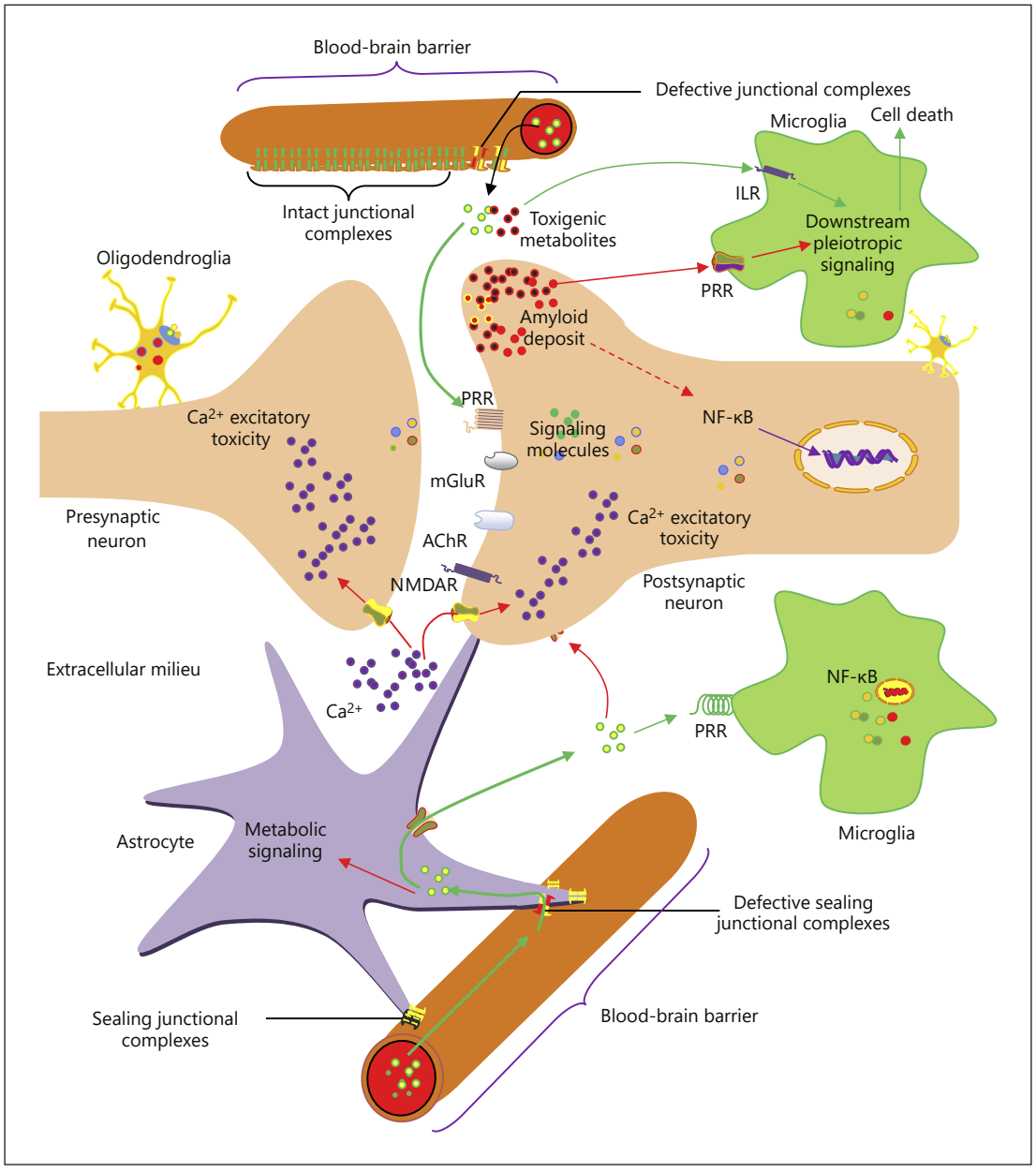
The increase in permeability of the intestinal and blood-brain barriers is critical to the transport of toxigenic metabolites to the brain (Fig. 2). Toxic metabolites such as trimethylamine N-oxide, D-amino acids, hippurate, phenylacetylglutamine, polyamines including putrescine, cadaverine, agmatine, and tyramine, acrolein, *p*-cresol sulfate, indoxyl sulfate, indole-3 acetic, phenol- and sulfur-containing compounds, as well as ammonia produced by the intestinal microbes can destroy the junctional complexes of the intestinal epithelial lining, thereby increasing the leakiness of the gut [151–165] (immune responses triggered by these microbial metabolites are integral to leaky gut [163–165]). This increases impairment in selective transport and paracellular shunt of substances between the gut and circulatory system, allowing for unregulated movement of biomolecules including toxins into the surrounding tissues and circulatory system from the luminal side of the gut (Fig. 2) [166].

The toxigenic metabolites can disrupt the endothelium of the blood-brain barrier by altering the expression of sealing claudins, which are supposed to preserve the permeability of the blood-brain barrier (Fig. 2, 3) [156, 167–170]. In addition, adherens proteins, membrane transporters, basal lamina, and extracellular matrix are affected [151]. Disorder in the expression of sealing claudins and other membrane components of the blood-brain barrier increases the development of neurodegenerative disorders due to unregulated translocation of toxic metabolites, leading to loss of neurons, astrocytes, microglia, endothelial cells, and pericytes (Fig. 3) [151, 171, 172]. Indeed, defects in blood-brain barrier components as well as glial cells have been observed in many neurodegenerative diseases including Alzheimer's disease [147, 173–186].

Decrease in Beneficial Intestinal Microbiota Metabolites is a Fundamental Factor in the Development of Dementia: Implication for New Therapeutic Options

The gut microbiota generates multiple biologically relevant molecules including vitamin K and the B group (B_1, B_2, B_3, B_5, B_6, B_8, B_9, and B_{12}), certain amino acids, polyphenols (including flavonoids), and short-chain fatty acids such as propionate, acetate, butyrate, valerate, isovalerate, and iso-butyrate, which modulate both peripheral and central processes to tissue or cellular injury [187–189]. The gut microbiota metabolites are either used locally by the epithelial cells of the gut or transported to different tissues and cells of the body via the circulatory system to exert an array of effects. Of particular interest are the short-chain fatty acids, which are metabolic products of the action of the intestinal microbiota on certain carbohydrates that are nondigestible by the host cells [190–193]. The short-chain fatty acids exert their effects on the host cells through the activation of G-protein-coupled receptors (GPR41, GPR43, and GPR109), modulating the activities of certain epithelial ion channels and neurohumoral responses of the gut and distant tissues and organs [194–197]. The short-chain fatty acids play a crucial neuromodulatory role in gut neuroendocrine cells and enterocytes, func-

tioning as chemotaxins, antioxidants, antitumorigens, antimicrobial and anti-inflammatory agents in the gut, and distant tissues including the brain [75, 197]. Dementia and other neurodegenerative disorders including some gut diseases are characterized by a significant decrease in the beneficial metabolites produced by the intestinal microbiota. Consequently, measures that will lead to elevation of these metabolites in the gut and bloodstream can enhance gut and brain functions in several diseases. The short-chain fatty acid propionate was shown to stimulate intestinal gluconeogenesis, decrease stress, and enhance memory. This short-chain fatty acid stimulates the G-protein-coupled receptor, free fatty acid receptor type 2, located on the epithelial cells of the gut and brain endothelium [171, 198–200]. Activation of the free fatty acid receptor on colonic enteroendocrine cells by the short-chain fatty acid can stimulate the recruitment of synaptic or membrane vesicle-loaded glucagon-like



peptide 1, peptide YY, and other neuropeptides towards the plasma membrane for exocytosis [201]. Furthermore, short-chain fatty acids such as propionate can halt infections by controlling CD14 signaling, suppressing the expression of low-density lipoprotein receptor-related protein 1, and reducing oxidative stress via activation of the nuclear factor (erythroid-derived 2)-like 2, a guardian of human lifespan that protects against ageing and diseases [171, 202, 203].

Both preclinical and clinical trials have shown the beneficial effects of the administration of agents that enhance the growth of intestinal microbiota [204–208]. Furthermore, emerging results of clinical trials have revealed immense benefits of the application of intestinal microbes in the treatment of disorders of the gut and brain [209, 210].

Clinical Trials on the Effects of Intestinal Microbiota and Related Products or Their Activators on Gut Health and Cognitive Functions

Transplantation or ingestion of specific intestinal microbiota and products that promote the growth of the beneficial microbes are increasingly gaining attention around the globe. For instance, preclinical trials of prebiotics, probiotics, and synbiotics have

Fig. 3. Translocation and generation of toxic metabolites to the neuroglial circuitry mediating cognitive functions. The toxins cause defects in the blood-brain barrier leading to increased translocation of more toxic metabolites and proinflammatory factors to the brain. These factors (e.g., proinflammatory cytokines and chemokines) mediate intracellular signaling that lead to protein and lipid breakdown, mitochondrial dysfunction, and disordered transport processes that culminate in neuroinflammation and neurodegeneration characterized for dementia and other brain diseases [120, 121]. For instance, dysbiosis has been associated with increased circulating neurotoxic interleukin mediators, which in turn predispose to the development of neurodegenerative diseases [6, 96]. Furthermore, ageing is associated with increased circulating neurotoxic mediators such as TNF-α, IL-6, and C-reactive protein, which can directly cause low-grade inflammation, that predispose the individual to the development of dementia and other diseases including diabetes [6]. The microbe-derived amyloids on the membrane of neurons, glia, and epithelial cells can stimulate pattern recognition receptors (PRRs) such as TLRs, causing local and possibly systemic inflammation, at least in part through their interaction with Peyer patches and other immune components of the gut [53]. Increased production of toxic metabolites by the activities of disordered gut microbiota has been implicated in metabolic disorders and local and systemic inflammatory responses [105–107]. As part of the toxic metabolites transported to the brain, amyloids can initiate a series of intracellular signaling via activation of PPRs such as RAGE, resulting in the activation of microglia [40] and phagocytosis of the amyloids [122, 123]. The binding of the metabolites or amyloids also initiate downstream signaling mediated via NF-κB pathways with resultant activation of the expression of proinflammatory cytokines, resulting in neuroinflammation, excitotoxicity, and oxidative stress [124, 125]. Pathological signaling of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α via the JAK-STAT (Janus kinase/signal transducers and activators of transcription) pathway in the central nervous system can disorganize microtubules via yet unknown mechanisms that lead to dysfunctions of microglia, the main immune sentinels of the central nervous system [126–129]. These microglia progressively lose the ability to clear cellular debris including amyloid proteins, which further stimulate signaling cascades that culminate in cell death [126, 127]. In the case of dementia due to Alzheimer's disease, the accumulating amyloid deposits provoke an inflammatory response that disorganizes the several protective mechanisms that favor neurodegeneration [38]. In addition, signaling pathways that initiate gene transcription such as p38 and other protein kinases are activated [127]. Furthermore, dysfunctions of amyloid peptide-degrading enzymes such as insulysin, neprilysin, and matrix metallopeptidase 9 have been reported in an animal model of dementia [128]. All these processes lead to neurodegeneration which favors the development of dementia or worsens the progression of the disease [124, 125]. It should be noted, however, that PRRs are regulated by molecules such as nucleotide-binding oligomerization domain (NOD)-like receptor (NLRs) and Toll-interacting protein (TOLLIP) among others [1, 3]. Toxigenic metabolites that favor the development of dementia and other neurodegenerative diseases may cause substantial defects in these regulatory peptides, thereby resulting to neuroimmune defects that underlie the development of the disease [1, 3].

shown promise for decreasing dysbiosis, and attenuating neuroinflammation and cognitive disorder. The beneficial effects of prebiotics, probiotics, and synbiotics are due to their action on the enteric nervous system, neuroendocrine system, and vagus, as well as spinal nerve fibers of the gut [204, 205, 207]. Certain microbial agents used as supplements to benefit the host are termed probiotics. Probiotics such as *Lactobacillus paracasei*, *L. acidophilus, L. casei, L. fermentum, L. helveticus*, *L. rhamnosus*, *Bifidobacterium bifidum*, *B. longum*, *B. breve*, and *B. infantis* enhance the central nervous system expression of BDNF, NMDA receptor subunits involved in LTP, synaptophysin, and other neuropeptides and synaptic components involved in synaptic and neural plasticity to improve memory and behavior, and decrease anxiety, depression, and a range of neurological and psychiatric disorders [97, 211–216]. Probiotics also affect the expression of neurotrophic factors in the enteric brain [213, 217].

The usefulness of probiotics is due to their pleiotropic signaling capabilities. They interfere with a range of cellular pathways implicated in the maintenance of homeostasis. For instance, oral probioticotherapy enhances the serum level of tryptophan, which is a precursor of serotonin [118]. Furthermore, an increase in the number of beneficial intestinal microbiota is due to the crucial influence of probiotics. In all, the effects of these beneficial microbes culminate in improved endocrine, immune, and neural signaling, and carbohydrate, protein, and lipid metabolism, which have a summative effect in the attenuation of neuroinflammation, thereby preventing neurodegeneration [218]. In a randomized, double-blind, controlled trial, it was revealed that a daily probiotic milk supplementation for 12 weeks in Alzheimer's type dementia patients resulted in a significant improvement in cognitive functions [205]. Evaluation of inflammatory markers showed their substantial reduction, while the patients' metabolic status showed improvement [205]. In another randomized controlled trial, Santocchi et al. [219] (2016) reported that probiotic supplementation in autistic patients resulted in a significant improvement in gut dysfunctions, cognition, and language. In their randomized, double-blind, placebo-controlled clinical trial on patients with major depressive disorder, Akkasheh et al. [204] (2016) reported that probiotic supplementation with *L. acidophilus, L. casei*, and *B. bifidum*, at a dose of 2×10^9 CFU/g each for 8 weeks, resulted in improvement in symptoms of depression and metabolic state, as well as a decrease in markers of oxidative stress and inflammation. These clinical trials have evidently shown promise for the application of the beneficial intestinal microbes for dementia therapeutics.

Prebiotics are nondigestible food components ingested by the host, but under the fermentative influence of the intestinal microbiota, they confer a range of health benefits to the host. Prebiotics are carbohydrate substances, mainly oligosaccharides. Substances with prebiotic effects include resistant starch, inulin, oligofructose, lactulose, galactooligosaccharides, xyloolidosaccharides, fructo-oligosaccharides, transgalactooligosaccharides, polydextrose, acacia gum, banana, psyllium, wheat dextrin, whole grain corn, and whole grain wheat [210, 213, 220–222]. Like the probiotics, prebiotics improve gut health, memory, and cognition, and decrease anxiety, depression, and stress [213, 222]. Prebiotics are associated with a decrease in microglial activation, and improvement in brain mitochondrial function and hippocampal plasticity. The result is attenuation of neuroinflammation and reduction in neurodegeneration [212]. Synbiotics are a combination of probiotics and prebiotics. Synbiotics also exert a profound beneficial influence on gut health and the central nervous system [212].

A new clinical trial revealed that a high initial dose followed by a lower daily maintenance dose of microbiota transfer therapy for 8 weeks results in improvement in intestinal microbiota composition and significantly reduces symptoms of gut and neurological disorders [210]. Analysis of a colony of intestinal microbiota over the therapy period revealed a

substantial increase in the beneficial microbes *Bifidobacterium*, *Prevotella*, *Bacteroides fragiles*, and *Desulfovibrio* [210]. Successful application of fecal microbiota transfer therapy is reported elsewhere [209]. An ongoing clinical trial "Microbiome and Dementia" on the effects of fecal microbiota transfer therapy on demented patients is currently underway (2017–2018) (ClinicalTrials.gov, NCT03167983).

Factors Influencing Intestinal Microbiota-Brain Cross-Talk

Several factors, mainly ageing, genetic, and environmental factors, influence the intestinal microbiota composition and functions as well as the brain to modulate processes that predispose to the development and progression of dementia [223–228]. Age, environment, and genes are important factors that determine or shape the development and progression of dementia and related neurodegenerative diseases [229]. Substantial changes in the composition of the intestinal microbiota and the gut functions occur during ageing [226–228], which may underlie age-related cognitive impairment or dementia. Certain changes in the genome or epigenome of the gut and brain cells may occur due to environmental insults. These changes can have enormous effects on the gut-brain, intestinal gut microbiota-gut and intestinal gut microbiota-brain axes [38].

Conclusion

The intestinal microbiota is a population of health-promoting microbes that controls a couple of cellular signaling pathways and metabolic processes via multiple mechanisms involving immune, neural, and neuroendocrine pathways. These pathways constitute a critical nexus between the intestinal microbiota and the brain. However, the intestinal microbes are affected by several factors, which may result in a reduction in the population of health-promoting microbes. The intestinal microbiota plays a critical role in the etiopathogenesis of neurodevelopmental, psychiatric, and neurodegenerative disorders. The association between disorder of the intestinal microbiota and dementia is due to the peculiar role of the metabolic products of the beneficial microbes together with their specific roles in the maintenance of both the intestinal and blood-brain barriers as well as regulation of local, circulating, and distant immunocytes, and enteric, visceral, and central neural functions. It is therefore imperative for studies investigating the impact of gut microbiota on gut and brain health to focus on multiple interrelated systems and organs involving local and central neuroendocrine, immunocyte, and neural signaling of microbial products and transmitter molecules of the intestinal residents and neurohumoral cells that not only maintain the gut, but also the integrity of the blood-brain barrier.

Disclosure Statement

There is no conflict of interest regarding the publication of this paper.

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