Journal of Research in Medical and Dental Science
2018, Volume 6, Issue 5, Page No: 246-263

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

The Gut Microbiota-brain Signaling: Behavioral Abnormalities of The Gut Microbiota Underlie Alzheimer's Disease Development and Progression. Dictatorship or Bidirectional Relationship?

Menizibeya O Welcome*

Department of Physiology, College of Health Sciences, The Nile University of Nigeria, Nigeria

ABSTRACT

Over the past decades, renewed research interest revealed crucial role of the gut microbiota in a range of health abnormalities including neurodevelopmental, neurodegenerative and neuropsychiatric diseases such as multiple sclerosis, autism spectrum disorders, and schizophrenia. More recently, emerging studies have shown that dysfunctions in gut microbiota can trigger the development or progression of Alzheimer's disease (AD), which is the most common neurodegenerative disease worldwide. This paper presents a state-of-the-art review of recent data on the association between dysfunctions of the gut microbiota and AD development and progression. The review stresses on the functional integrity and expression of sealing and leaky junctional complexes of the intestinal and blood-brain barriers as well as contemporary understanding of the multiple mechanisms that underlie the association between barrier dysfunctions and β-amyloid accumulation, resulting to neuro inflammation and subsequently, progressive decrease in cognitive functions. Key determinants of cerebral amyloid accumulation and abnormal gut microbiota are also discussed. Very recent data on the interaction of the gut microbiota and local/distant immunocytes as well as calcium signaling defects that predispose to AD are also discussed. Both germ free animal models of AD and human subjects have shown that senescence, diseases, genetic and epigenetic modifications, and environmental hazards predispose to substantial reduction in composition of beneficial microbes, particularly Firmicutes and Bacteroidetes phyla and increase proinflammatory bacteria of the Proteobacteria phylum. Finally, emerging treatment with different types of psychobiotics and their limitations are highlighted. The gut microbiota-brain bidirectionality in intestinal dysfunctions and AD etiopathogensis is also discussed.

Key words: Alzheimer's disease, Gut microbiota, Microbiota-gut-brain axis, Gut-brain axis

HOW TO CITE THIS ARTICLE: Menizibeya O Welcome*, The gut microbiota-brain signaling: Behavioral abnormalities of the gut microbiota underlie alzheimer's disease development and progression. Dictatorship or bidirectional relationship? J Res Med Dent Sci, 2018, 6 (5):246-263

Corresponding author: Menizibeya O Welcome
e-mail✉: welcome.menizibeya@nileuniversity.edu.ng
Received: 03/09/2018
Accepted: 03/10/2018

INTRODUCTION

The functional connectivity or association between gut and brain was first proposed by the Ancient Greek philosophers and scientists. During this time, disease of the brain such as epilepsy was thought to result from dysfunctions of the gut. Consequently, it was treated by deprivation of food ingestion. Unfortunately, however, for several centuries, no much attention was given to the gut-brain functional relationship until the late nineteenth century when this functional connectivity was revived. The twentieth and twenty first centuries have witnessed a tremendous burst in interest on the gut-brain functional connectivity, which is now believed to underlie the development of several human ailments [1,2].

Under normal conditions, the gut microbiota maintains functional and structural integrity of the gut mucosa as well as homeostasis of not only the gut, but also other organs and tissues of the body [3,4]. Over the past decades, accumulating evidences have implicated dysfunctions of the gut microbiota in the pathogenesis of many diseases of the brain, including depression, anxiety, autism spectrum disorders, attention deficit hypersensitivity disorder, and multiple sclerosis [3,5–7]. More recently, emerging studies have shown that dysfunctions of the gut microbiota can trigger the development of Alzheimer's disease (AD) or worsen the progression of this neurodegenerative disease [8-10]. However, due to the bidirectionality of the gut-brain axis, it is not clear whether AD can predispose an individual to disorders in gut microbiota.

AD is the most common, chronic neurodegenerative disease, mostly affecting medial temporal lobe (particularly, hippocampus) and associative neocortex, and is characterized by excessive neuronal accumulation of a 38–43 amino acid amyloid-beta peptide (Aβ), due

to failure of the compensatory mechanisms that prevent its aggregation, ultimately leading to neurodegeneration and dementia, with formation of senile (neuritic) plaques, and excessive phosphorylation of the cytoskeletal Tau proteins mostly in neurons, which accumulate to form neurofibrillary tangles [11–13]. The accumulation of Aβ in neurons is due to multiple disorders of homeostasis that regulate the cleavage of the amyloid precursor protein (APP). The cleavage reaction is successively executed by beta-secretase and gamma-secretase (Figure 1) [12].

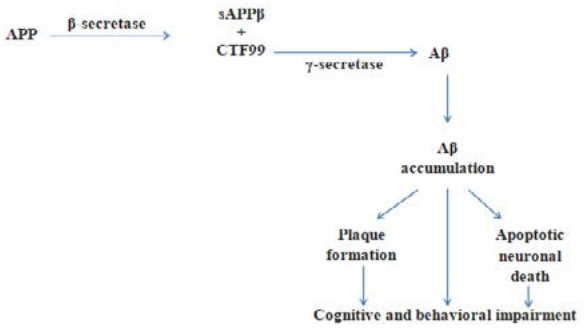

Figure 1: Sequence of events resulting to the formation of beta-amyloid protein (Aβ) and plague that lead to neurodegeneration and dementia

In Figure 1, the amyloid precursor protein (APP) is cleaved by the transmembrane enzyme, β-secretase, to produce soluble amyloid precursor protein-β (sAPPβ), and carboxy-terminal fragment 99 (CTF-99). The latter is worked upon by another intramembrane bound protease, γ-secretase, resulting to the formation of amino-terminal APP intracellular domain and Aβ, which accumulates in the neuron, due to dysfunctions of the compensatory mechanisms that prevent its aggregation, and subsequently oligomerize and forms plaques. The formation and accumulation of Aβ and plaques underlie the cognitive and behavioral impairment, which AD patients' experience [11,12,14–18].

The sequence of events outlined in Figure 1 leads to progressive cognitive and behavioral impairment that culminates in functional dependence, and subsequently, death [17–24].

Despite significant progress made in understanding the mechanism of amyloid formation, which underlies the pathogenesis of AD [25–27], surprisingly however, there is no effective therapy for AD [28,29]. Current therapeutic options include use of cognitive enhancers (acetyl-cholinesterase inhibitors donepezil, extended release galantamine hydrochloride, and the N-methyl-D-aspartate receptor antagonist memantine) [30,31]. Relatively more recently, the addition of healthy diet, physical and cognitive training to the treatment regimen have shown to improve symptoms of the disease [11]. Success in development of β- and γ-secretase inhibitors, which would have been effective therapeutic agents, has shown detrimental effects due to inhibition of notch signaling pathway. A promising class of pharmacological agents for AD, γ-secretase modulators, does not interact with the notch pathway, and thus may be a safer option for AD pharmacotherapy [31]. Furthermore, classification of the disease into different phases: pre-symptomatic (pre-clinical), pre-dementia (progressive, mild cognitive impairment), and clinically-defined dementia [12], which was believed to enable early identification of individuals at risk and enhance management of the disease, has not had any positive impact on the incidence rate of the disease [32,33]. More so, recent development of robust biomarkers of AD, which is thought to provide improved diagnostic accuracy and prediction to identify individuals at risk, thereby initiating early treatment and enhancing rate of decline in phase conversion of the disease [12,34,35]. Unfortunately, however, there is a continuous rise in the incidence of the disease [32,33].

The continuous search for different treatment options of AD or the prevention of the disease provides a substantial argument for constantly rising prevalence of AD in the world [36]. Over the past decades, there has been continuous increase in the prevalence of AD and the trend is believed to continue in the nearest decades [37]. Alzheimer's Disease International revealed that between 1990 and 2017 there has been constant increase in the incidence rate of the disease [32]. In 2006, the prevalence of AD in the world was approximately 26.6 million [33]. In 2013, about 44.4 million people had AD, and the number of people suffering from AD is believed to steadily increase, hitting 75.6 million in 2030 [32], and by 2050, the prevalence of AD is estimated to reach 106.4 million–This means that 1 in every 85 persons worldwide will have the disease by 2050 [33]. It should be noted, however, that prevalence of the disease may substantially vary in different regions of the world, ranging from 3 to 15%: Takizawa et al. reported 3%–7% prevalence [38], Chandra et al. identified a prevalence of 10.5% [39], and 15% was documented by Ganguli et al. [40]. Throughout the world, accumulating reports have shown that the incidence of AD will continue to increase [32,36].

The mortality rate from the disease is very high. Millions of AD patients are estimated to die annually as new cases are continuously recorded in different parts of the world [41]. While the proportion of deaths from other non-communicable diseases (heart disease and stroke) between 2000 and 2010 reduced by 16% and 23% respectively, the proportion of deaths from AD was reported to increase by 68% [42]. The financial burden of AD on caregivers, families and the health care system is substantially high [41,43–45]. For instance, in the United States alone, total costs of AD was estimated at 183 billion United States (US) dollars in 2011 [30], caregiver cost in 2014, estimated at more than 217 billion US dollars [46] and is expected to increase to 1.1 trillion US dollars by 2050 [30].

Recent investigations highlighting the role of the gut microbiota in development and progression of AD, indicates that the gut and its commensal microbes represent a key therapeutic target for AD [8–10,47,48]. This paper reviews recent data on the association between dysfunctions of the gut microbiota and AD development and progression. The paper also presents contemporary understanding and state-of-the-art information on the mechanisms for this association. Since disorders in gut microbiota can lead to AD development, question arises-whether AD can predispose an individual to disorders in gut microbiota. Future research directions are explored at strategic points of the discussion.

Microecology of the gut microbiota: Normal and abnormal gut microbiota

Normal gut microbial ecology

The gut microbiota refers to the overall beneficial microbial population that inhabits the entire gastrointestinal tract, but can be potentially harmful to the host in unfavorable micro-environmental conditions. The gut microbiota constitutes over 90% of the total microbes that colonize the human body. This peculiar feature of microbial colonization of the gut is evolutionarily determined and may be due to the favorable gut microenvironment and availability of nutrients [49,50].

Colonization of the gut is believed to begin in utero when the fetus swallows amniotic fluid, which is now believed to harbor specific commensal microbes [51,52], contrary to the long held view that this fluid was sterile [53,54]. Microbial colonization of the baby increases substantially following birth and is believed to depend on several factors including mode of delivery, and other environmental and genetic factors [55]. By 3 years of age the child's microbial composition of the gut is similar to the adult composition [48].

The adult gut contains approximately 100 trillion beneficial microorganisms comprising about 1000 species mainly from bacteria and archaea [56]. Majority of the gut microbiota comprises the Firmicutes and Bacteroidetes species, but also, a smaller number of *Actinobacteria, Cyanobacteria, Fusobacteria, Proteobacteria,* and *Verrucomicrobia* (Tables 1A-1C) [57–59]. This classification (Tables 1A-1C) is based on phylogenetic data. However, a recent functional classification of microbes based on their interactions

Table 1A: Nomenclature of the most abundant bacteria (*Bacteroidetes*) found in a healthy gut [68–71]

Class	Family	Genus
Bacteroidia	*Bacteroidaceae*	*Bacteroides* sp. (*B. fragilis, B. helcogenes, B. salanitronis, B. thetaiotaomicron, B. vulgatus, Parabacteroides* sp.)
	Porphyromonacaceae	*Odoribacter splanchnicus, Dysgonomonas* sp., *Porphyromonas* sp., *Bamesiella* sp., *Tannerella* sp.
	Rikenellaceae	*Alisitpes* sp. (e.g. *A. putredinis, A. finegoldii, A. onderdonkii and A. shahii), Rikenella sp., Acetobacteroides* sp., *Anaerocella sp.*)
	Prevotellaceae	*Prevotella* sp., *Paraprevotella* sp., *Alloprevotella* sp., *Hallella* sp., *Marseilla* sp., *Metaprevotella* sp.

Table 1B: Nomenclature of the most abundant bacteria (*Firmicutes*) found in a healthy gut [60,68–80]

Class	Family	Genus
Bacilli	*Streptococcaceae*	*Streptococcus* sp. (*S. dysgalactae, S. gordonii, S. agalactiae*)
	Bacillaceae	*Bacillus* sp. (e.g. *B. timonensis*)
	Lactobacillaceae	*Lactobacillus* sp. (e.g. *L. casei, L. rhamnosus, L. fermentum, L. plantarum, L. salivarius, L. bulgaricus, L. acidophilus, L. leichmannii*)
	Palanococcaceae	*Kurthia senegalensis, K. massiliensis, K. timonensis*
	Enterococcaceae	*Enterococcus* sp. (e.g. *E. saccharolyticus*)
	Paenibacillacaceae	*Paenibacillus* sp.
	Listeriaceae	*Listeria grayi*
	Leuconostocaceae	*Weissella* sp., *Leuconostoc mesenteroides*
Clostridia	*Clostridiaceae*	*Clostridium* sp. (e.g. *C. leptum, C. ramosum, C. orbisindens, C. saccharolyticum, C. defficile*)
	Ruminococcaceae	*Ruminococcus* sp. (e.g. *R. albus, obeum or Blautia obeum, R. massiliensis, R. torques, R. bromii*), *Flavonifractor, Acetanaerobacterium, Anaerobacterium, Anaerofilum, Ethanoligenens Faecalibacterium*
	Eubacteriaceae	*Eubacterium* sp. (e.g. *E. limosum, E. ballii, E. ventriosum, E. eligens, E. rectale*), *Acetobacterium, Alkalibacter, Alkalibaculum, Anaerofustis, Garciella, Pseudoramibacter*
	Lachnospiraceae	*Dorea* sp., *Anaerostipes* sp., *Blautia* sp., *Coprococcus* sp., *Roseburia* sp., *Butyrivibrio* sp., *Marvinbryantia* sp., *Roseburia hominis*
	Peptococcaceae	*Desulfitobacterium* sp., *Desulfonispora* sp., *Desulfotomaculum* sp., *Peptococcus* sp.
	Peptostreptococcaceae	*Peptostreptococcus productus, Anaerococcus senegalensis*
	Clostridiales Family XI, Incertae Sedis	*Parvimonas* sp., *Finegoldia* sp.
	Christensenellaceae	*Christensenella minuta, C. timonensis, C. massiliensis*
Negativicutes	*Veillonellaceae*	*Negativicoccus* sp., *Veillonella* sp. (e.g. *Veillonella parvula*), *Dialister* sp., *Megamonas* sp., *Mitsuokella* sp., *Massilibacillus* sp.
	Acidaminococcaceae	*Acidaminococcus* sp.
	Selenomonadaceae	*Propionispira* sp., *Selenomonas* sp., *Zymophilus* sp.
Erysipelotrichai	*Erysipelotrichaceae*	*Corpobacillus* sp., *Holdemania* sp., *Catenibacterium* sp., *Turicibacter* sp., *Dielma fastidiosa*

Table 1C: Nomenclature of the other bacteria found in the gut [60,68–80]

Phylum	Class	Family	Genus
Actinobacteria	*Actinobacteria*	*Corynebacteriaceae*	*Corynebacterium* sp. (*C. ammoniagenes, C. parvum, C. pyogenes*), *Turicella* sp.
		Coriobacteriaceae	*Eggerthella* sp., *Collinsella* sp., *Slackia* sp., *Denitrobacterium sp., Parvibacter* sp.
		Propionibacteriaceae	*Ponticoccus* sp., *Proponiobacterium* sp., *Gordonibacter* sp., *Propioniferax* sp., *Tessaracoccus* sp., *Naumannella* sp.
Euryarchaeota	*Methanobacteria*	*Methanobacteriaceae*	*Bifidobacteria* sp., *M. smithii*
Verrucomicrobia	*Verrucomicrobia*	*Verrucomicrobiaceae*	*Akkermansia municiphila*
Fusobacteria	*Fusobacteria*	*Fusobacteriaceae*	*Fusobacterium* sp.
Synergistetes	*Synergistia*	*Synergistaceae*	*Synergistes* sp., *Anaerobaculum hydrogeniformans, Aminobacterium* sp.
Proteobacteria	*Gammaproteobacteria*	*Enterobacteriaceae*	*Escherichia coli, Salmonella* sp., *Yersinia pestis, Klebsiella* sp., *Shigella* sp., *Proteus* sp., *Enterobacter* sp., *Serratia sp., Providencia sp., Edwardsiella sp., Cedecea sp., Citrobacter* sp.
		Moraxellaceae	*Acinetobacter radioresistens*
		Succinivibrionaceae	*Succinatimonas* sp.
		Desulfovibrionaceae	*Desulfobivrio* sp., *Bilophila* sp.
		Pseudomonadaceae	*Pseudomonas* sp.
	Deltaproteobacteria	*Desulfovibrionaceae*	*Desulfovibrio piger, Bilophila wadsworthia*
	Epsilonproteobacteria	*Helicobacteraceae*	*H. pylori, H. windhamensis, H. cinaedi, H. pullorum*
		Campylobacteraceae	*Campylobacter* sp., *Arcobacter butzleri*
	Betaproteobacteria	*Neisseriaceae*	*Neisseria macacae*
		Oxalobacteraceae	*Oxalobacter* sp.
		Burkholderiaceae	*Ralstonia* sp.
		Sutterellaceae	*Sutterella parvirubra, parasutterella excrementihorminis*

with the host immune system was proposed [60]. These resident microbes of the gut inhabit every region of the tract–from the mouth to the anus. The mouth is estimated to harbor approximately 500–700 bacterial species mainly from *Actinomyces, Fusobacterium, Granulicatella, Gemella, Haemophilus, Neisseria, Porphyromonas, Rothia, Streptococcus,* and *Veillonella* [61,62]. The esophageal microbiota population mainly comprises *Actinobacteria, Bacteroidetes, Firmicutes,* and *Proteobacteria* [63,64]. The estimated number of gut microbiota steadily increases aborally [65,66]. The resident microbes of any region of the gut can substantially influence the state of health and development of diseases through broadly defined microbe-microbe and microbe-host interactions [67].

The normal composition of gut microbiota strongly depends on many factors, which include inter-individual differences [60,68,81,82], age, disease, antibiotic use [68,82], malnutrition, and dietary habit [68] (discussed in the subsections below). For example, vegetarians have elevated number of *Bacteroidetes*, but decreased quantity of *Clostridia*. Also, different ethnic groups and geographical regions have variations in composition of gut microbiota [68]. So, Americans, Asians, and Europeans only have in common, symbiotic bacteria of *Sesbania Scop, Dictyostelium discoideum,* and *Schizosaccharomyces* pombe [68]. Wide differences in gut microbiota have been reported amongst native Africans, African Americans, native Europeans, and European Americans [81]. Within geographical location, climate and latitude appear to be crucial factors that determine differences in colonization of gut microbiota in individuals of different races [81]. Further details on gut microbiota differences according to geographical locations have been discussed in a study by Gupta et al. [83].

Abnormal gut microbial ecology in Alzheimer's disease

Abnormal microbes arise in the gut following disturbances by factors that perturbs the normal gut microbial ecology. Such factors mainly include, type of nutrition, diet, pathogenic infections, and antibiotics use [8,9]. Abnormal microbiota is characterized by the presence of pathogenic microbes and substantial reduction in the proportion of the beneficial microbes in the gut. In abnormal conditions of the gut microenvironment, species of the phylum *Proteobacteria* such as *Clostridium, Escherichia*, and *Shigella* (proinflammatory bacteria) are expected to increase [47,48,84,85]. In contrast, anti-inflammatory bacteria, in particular, *Eubacterium rectale, Bacteroides fragilis, Bifidobacterium breve, B. longum, B. infantis, Lactobacillus helveticus, L. rhamnosus, Prevotella, Desulfovibriobacteria*, and the genera belonging to the family *Lachnospiraceae*, and *Ruminococcaceae* are substantially reduced in abnormal gut microbial ecology [47,48,84–89]. Recent report has implicated the gastric cancer causing microbe, *Helicobacter pylori* in the development of Alzheimer's disease due to encephalitogenic responses of the pro-inflammatory Th17-cells that develop in response to *Helicobacter pylori* infection [86,87]. Very recent studies using germ free mice models of AD have been used to clarify how the gut microbiota changes in AD. Zhan et al. [90] reported association between cognitive dysfunction and abnormal gut microbiota in senescence-accelerated mice. In a recent study conducted in a Drosophila AD model by Wu et al. not only showed that

abnormal (or pathogenic) microbes in the gut resulted to neuroinflammation, they also reported exacerbation of progression of Alzheimer's disease following enteric dysbiosis through increased recruitment of immune hemocytes to the brain, which resulted to induction of neurodegeneration via TNF/JNK (tumor necrosis factor/ c-Jun N-terminal kinase) pathway [91]. Other authors have identified similar reduction of the composition of beneficial bacteria in AD animal models. Indeed Harach et al. reported a significantly higher (by 24%) cerebral level of amyloid beta protein (Aβ42) in germ free mice model of AD compared to conventionally-raised transgenic mice model of AD [86]. Furthermore, Harach et al. [86] showed that *Actinobacteria, Firmicutes, Verrucomicrobia*, and *Proteobacteria* were significantly lower in conventionally-raised transgenic mice model compared to wild type. The conventionally-raised transgenic mice had significantly reduced *Allobaculum* and *Akkermansia*, but increased number of the genera in Rikenellaceae, compared to the wild type [86]. However, the conventionally-raised transgenic mice model had a higher number of *Bacteroidetes* and *Tenericutes* phyla compared to aged mice model, suggesting that age remains a crucial factor that predisposes to the development of the diseases [86]. Human data have also revealed similar findings [48]. Recent experimental results in animal models and human subjects have shown that improving abnormal gut microbiota may provide an alternative treatment for cognitive dysfunction and AD (vide infra) [90].

Factors modulating the gut microbiota-brain axis influence the development and progression of Alzheimer's disease age-related factors

The major factor modulating the development or progression of AD is aging (Figure 2). The biological phenomenon of normal ageing is accompanied by several alterations in cerebral metabolism [92,93]. The metabolic alterations arising from normal ageing include decreased glucose transport and utilization, resulting to ATP depletion, which in turn affects signaling of Ca^{2+} and neurotransmitters (e.g. glutamate) and their receptors [92,94]. Disorder in brain metabolism due to ageing increases neuronal Ca^{2+} level and glutamate toxicity, which favor accumulation of Aβ [92,95]. Normal biological ageing is also accompanied by substantial decrease in antioxidants and elevation of free radicals, which worsen the development or progression of AD [92]. In addition, accumulation of Aβ increases with age [95]. The impact of ageing on brain cells, in addition to the gut microbiota changes associated with ageing substantially worsens the prognosis of AD [92,94].

As shown in Figure 2, Homeostatic disorders resulting from ageing, genetic, and environmental influences as well as other factors, contribute to derangement in metabolism, immune and neural signaling, that subsequently favor the generation of Aβ peptides and its accumulation in the extracellular spaces of brain cells, and cytoplasmic tau protein hyperphosphorylation. These processes mostly occur in neurons (e.g. cholinergic neurons), but they can take place in astrocytes and other glial cells, especially in condition of stress that results in the activation of glial cells [17,19]. At first, the deposition of Aβ and tau aggregates triggers the activities of the neuronal and glial cytoplasmic debris clearance system, known as proteolytic system–autophagy and ubiquitin-proteasome system [20]. But the proteolytic system become overworked or subsequently, progressively destroyed by the disease. Indeed several protein types, including proteins of the proteolytic system, have been

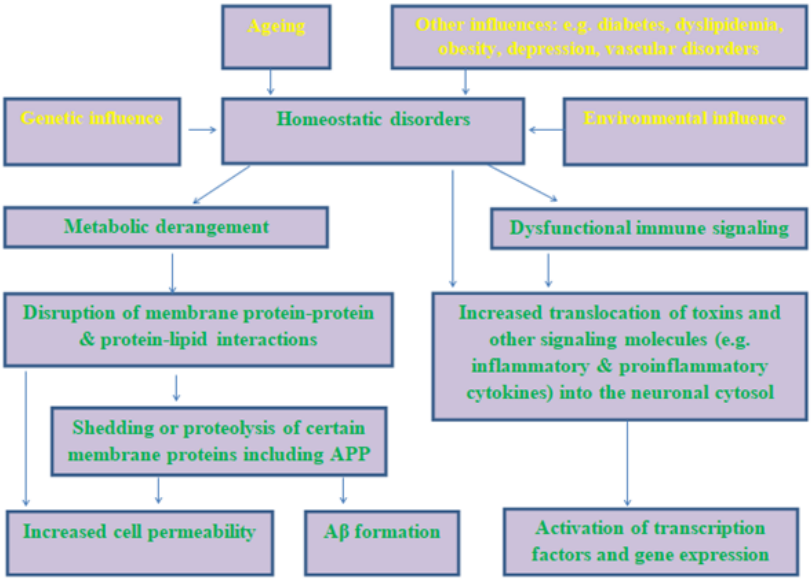

Figure 2: Sequelae of events that favor the formation of Aβ peptides and Homeostatic disorders resulting from ageing, genetic, and environmental factors

found to accumulate in the cytosol in AD [21]. Another compensatory mechanism involves an increase in the expression of the anti-inflammatory, neuroprotective interleukin-10 [22]. Failure of the compensatory mechanisms finally leads to continuous accumulation of Aβ and tau aggregates, which in turn leads to neuronal and glial cell damage, and further exacerbates the inflammatory and oxidative stress in neurons and glia [19]. The brain regions affected, which mostly involve the hippocampus and neocortex, play essential role in cognition, precisely, conscious memory of facts and events. The hippocampus and associated structures of the medial temporal lobe form the limbic system, which is involved in the development of anxiety, depression and other behavioral abnormalities [23,24].

Genetic factors in Alzheimer's disease

Mutations in genes localized on chromosomes 14, 19, and 21 that code for APP and presenilin have been implicated in AD development. The peptide presenilin is the catalytic subunit of γ secretase. Active γ secretase complex is formed from presenilin 1 or 2, nicastrin, presenilin enhancer 2 and anterior pharynx defective 1 [15,17,92,96-98]. Hundreds of autosomal dominant mutations have been identified in APP and presenilin [17]. A patient with an AD causing mutation can have the mutation affecting either APP or presenilin, or a combined mutation affecting both proteins. It is believed that the majority of early-onset cases of AD results from a combination of genetic mutations that affect both APP and presenilin proteins [20]. It should be mentioned that not all mutations in genes encoding these proteins may lead to disease development. Pathogenic mutations of the APP gene have been reported in different populations– These mutations increase Aβ generation by promoting APP β-site cleavage by beta-secretase [99,100]. However, a protective mutation of APP gene has been reported, known as the Icelandic mutation, which decreases the generation of Aβ [101,102]. Such protective genetic alteration can be harnessed for potential benefit that may add to the effectiveness of AD treatment or disease prevention. Genetic disorders in cerebral metabolism can enhance the rate of accumulation of Aβ due to disordered Ca^{2+} signaling [95].

Environmental factors

Some environmental factors contribute to the development and progression of AD (Figure 2) [103,104]. For instance, unhealthy early- and late-life exposure to environment substances that negatively affects the composition of the gut microbiota may be possible factors that affect the development and progression of AD [105]. Toxic environmental substances such as lead, mercury, pesticides, and other noxious substances can cause neurotoxicity that leads to serious neurological disorders. These toxic substances cause senescence to occur at a faster rate, which may in turn facilitate Aβ formation [28]. To prevent the detrimental effects of environmental factors on the formation of Aβ, experts recommend a healthy diet, nutrition, and physical activity, which are effective in reducing the incidence of the disease [11,106]. Lower incidence of AD has been associated with a lower consumption of dairy products. The consumption of fruit and vegetable was reported to protect against cognitive decline, dementia, and AD. The Mediterranean diet, which comprises monounsaturated fatty acids, polyunsaturated fatty acids, cereals and red wine, was associated with decreased cognitive decline and phase conversion of AD [107–109]. Emerging studies have also reported the beneficial effect of low-moderate alcohol consumption on cognitive decline, dementia and AD [108,110]. However, it should be mentioned that recent evidences indicate the absence of safe quantity of alcohol consumption. Thus, defining quantity of alcohol intake as low or moderate may not be strictly correct [111,112]. The recent global analysis performed by the Global Burden of Disease Study 2016 Alcohol Collaborators revealed a high level of alcohol-related harm and mortality even at a low alcohol consumption [112], confirming our previous results [112–114]. It is, therefore, necessary to investigate the mechanisms of action of alcohol, even in low-moderate doses, especially on the central nervous system functions.

Individual factors

The composition and type of gut microbiota substantially vary among individuals and depends on many factors such as nutrients, lifestyle, age, antibiotics, infections, genetic factors, mode of delivery at birth, method of infant feeding mucosal receptors, luminal pH, and immune response [50,66,115,116]. Some of these factors modulate the risk for several brain diseases including AD [117]. Thus individual microbial population differences may underlie differences in Alzheimer's disease development and progression.

Other factors

Other factors such as diabetes mellitus, obesity, hyperlipidemia, vascular dysfunctions, depression, and stress tend to play a role in the development or progression of AD (Figure 2) [56,93,105,118–120]. Also, sex and level of education have been shown to influence the development of AD [40,108]. However, certain forms of AD, which may not have identifiable cause, may be related to multiple factors [92,121,122].

The multiple pathways that connect the gut microbiota to the brain

The pathways and mechanisms that link the gut microbiota to the brain are multiple and complex, generally termed the microbiota-gut-brain axis, a bidirectional communication network that comprises endocrine, neural, immune, and metabolic functional connectivity [8,9]. This network is essential for the maintenance of homeostasis in the gut and almost all other organs and tissues of the body [123]. The endocrine pathway is mediated by the interaction

between the gut microbiota and neuroendocrine cells of the gut. The neural pathway is mediated by interaction of the gut microbiota with central nervous system (including hypothalamic-pituitary-adrenal axis), autonomic nervous system (mainly via the vagus nerve), and enteric nervous systems. The immune pathway is due to the interaction between the gut microbiota and neuroimmune systems [123,124]. The metabolic pathways involve the synthesis of metabolites by the gut microbiota such as short chain fatty acids that regulate a range of physiological processes in the gut and other regions of the organism [124,125].

Mechanisms underlying abnormal gut microbiota behavior resulting to Alzheimer's disease development and progression: Implications for new therapeutic options

Gut barrier defect due to abnormal microbial ecology

Abnormal microbes in the gut produce toxins that disrupt the intercellular linkages between epithelial cells of the gut thereby increasing the rate of paracellular shunt of substances between the gut and circulatory system (Figure 3) [9]. One of the most implicated intercellular linkages in this disruption is the tight junction proteins (claudins), resulting to disorder of the gate and fence function of tight junctions (Figure 3). This leads to impairment in selective transport of substances, allowing diffusion of proteins and lipids as well as uncontrolled movement of ions and toxins into the circulatory system from the luminal side of the gut (Figure 3). This increases the leakiness of the gut epithelium due to increased expression of claudin-2 [126–132]. The abnormal gut microbiota also disrupt the permeability of the blood-brain barrier (Figure 3) due to disorder in the expression of sealing claudins type-1, -3, -4, -5, -7, -8, -11, -14, -15, -16, -18, and -19, which are supposed to preserve the permeability of the blood brain barrier [128,133–137]. Disorder in the expression of leaky and sealing claudins increases the likelihood of development of neurodegenerative disorders, including AD [9,133,134].

In Figure 3, the payer's patch and the subepithelial dome containing high number of immune response cells participate in response to foreign aggression. Microbial antigens, toxins and other proinflammatory factors diffuse to neighboring cells (including interstitial cells of Cajal, enteric neurons and glia), tissues and organs via the circulatory system and can exert a range of influences on vagus nerve signaling. The toxins and proinflammatory factors reach the brain mainly *via* the circulatory system or affect brain information processing via influences on the vagus nerve signaling.

Gut microbiota–immune axis dysfunctions contribute to the development and progression of Alzheimer's disease

The gut microbiota actively coordinates the activity of the immune system, in part, by maintaining the intestinal barrier [47,88]. Over the past decades research has shown that disorder in intestinal immune response is associated with defect in gut permeability [47]. In such conditions there is usually increased levels of interleukin (IL)-1, IL-6, tumor necrosis factor-α, and interferon-γ [47,125]. These immune factors not only activate local immunocytes and cells of the enteric brain, but also, distant immunocytes as well as microglia and astrocytes in the central nervous system (Figure 4) [125]. In Drosophila AD model, Wu et al. reported that enteric infection resulting to gut dysbiosis increased the movement of both local and distant immunocytes such that these cells were more readily attracted to the brain, thereby worsening the progression of AD [91]. Interestingly, genetic depletion of the immunocytes lead to attenuation of neuroinflammation, and consequently, alleviated neurodegeneration [91].

The abnormal (pathogenic) gut microbiota produce high quantities of lipopolysaccharides, peptidoglycan,

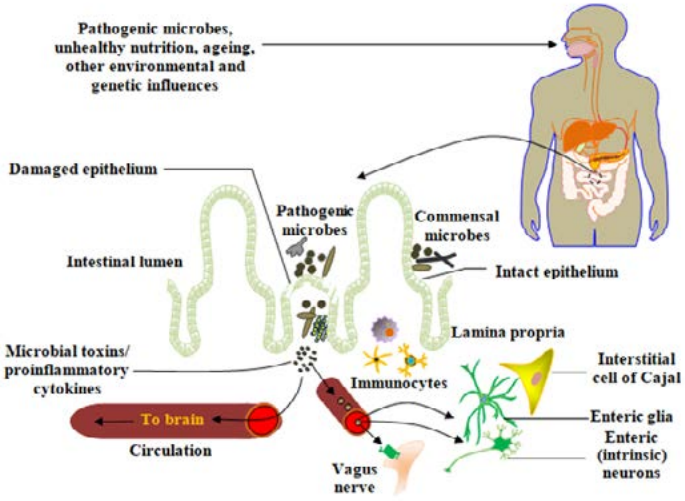

Figure 3: Factors (invasion by pathogenic microbes, unhealthy nutrition, ageing, and other environmental and genetic factors) that disrupt commensal microbes of the gut result to damaged epithelium

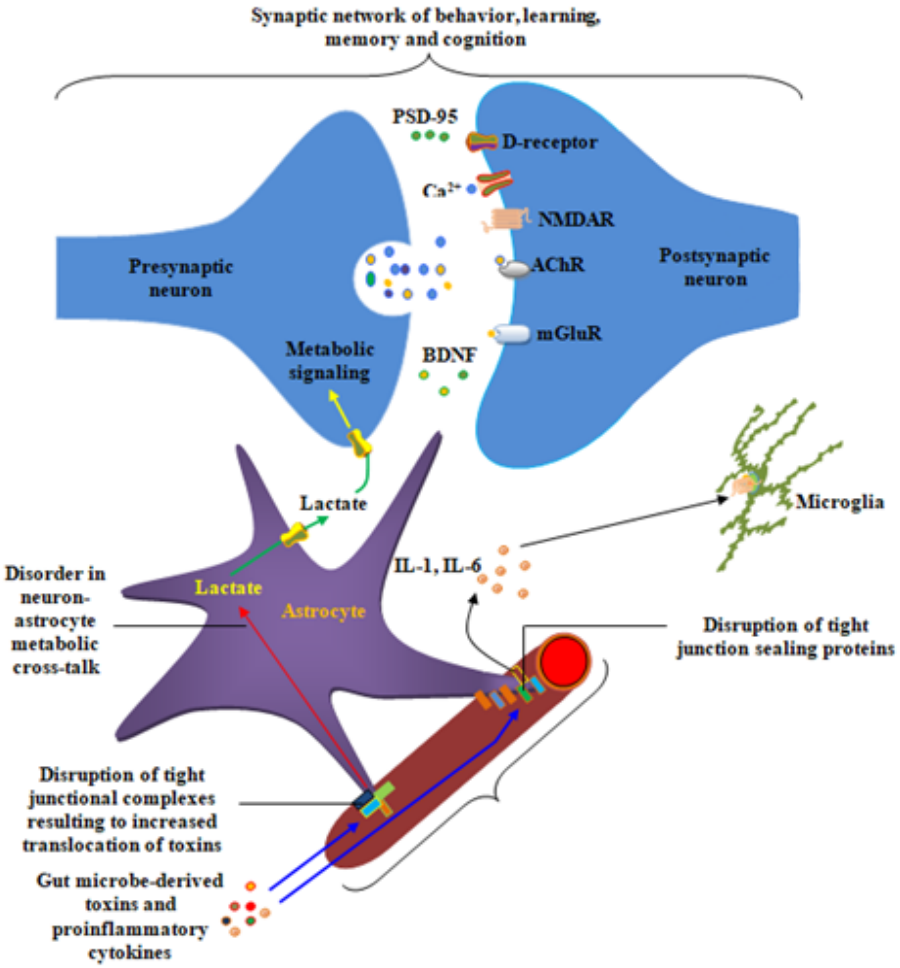

Figure 4: Neuroastroglial signaling of microbial toxins and proinflammatory cytokines disrupt synaptic network of behavior, learning, memory and cognition, underlying the onset of AD development

lipoteichoic acid, teichoic acid, lipoarabinomannan, arabinogalactan, lipopeptides, flagellin, and foreign nuclear materials 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 [8,138,139]. These structural motifs, which are associated with pathogenic microbes, are known as pathogen-associated molecular patterns, PAMPs. PAMPs are sensed by pattern recognition receptors (PRRs) of the host cell plasma membrane. Toll like receptor (TLR) is an example of PRRs. PRR can also sense cell damage by recognizing substances released upon cell damage, called damage-associated molecular patterns, DAMPs [140–143]. DAMPs include certain extracellular matrix components released during cell damage (e.g. laminin, elastin and collagen-derived peptides, fibronectin, matrix metalloproteinase-3 and -13, versican, and biglycan) and cytoplasmic proteins such as heat shock proteins, RNA and mitochondrial DNA, nuclear DNA, IL-1, high mobility group box 1 protein, histones, adenosine triphosphate, and antimicrobial peptides [144–147].

TLRs recognize pathogenic microbes by binding to PAMPs or DAMPs, with resultant activation of transcription factors such as nuclear factor kappa of B cell including the interferon regulatory factors, leading to the synthesis of cytokines, and interferons [140,144,147]. The cytokines exert their activities on the cell mainly *via* JAK-STAT pathway [140,147,148].

It should be mentioned, however, that there are multiple pathways through which the cell recognizes pathogenic microbes. The pattern recognition molecules MBL (mannose-binding lectin) and ficolins functioning as opsonins link up with MBL-associated serine protease-2 (MASP-2), forming MBL-MASP-2 complex, which recognizes and subsequently binds to carbohydrate molecules (e.g. N-acetylglucosamine) of bacterial cell wall to initiate series of reactions [149–152]. Initially these reactions are supposed to control the activity of the pathogenic microbes, but subsequently result in excessive production of immune factors (including proinflammatory cytokines), which in turn leads to altered balance or composition of the gut microbiota, and increased intestinal permeability [152,153], thereby promoting the transport of these cytokines into circulation [93]. The proinflammatory cytokines can be transported to different tissues including the brain,

initiating neuroinflammatory process and synthesis of amyloid proteins, which can trigger the development or progression of AD [8,124]. Furthermore, certain abnormal microbes of the gut, known as amyloidogenic bacteria, can produce amyloid proteins, which contribute to the development or progression of AD [8].

It should be noted, however that not only intestinal immune responses, but also liver innate immune responses immensely contribute to the regulation of gut immune activity. The liver is a crucial innate immune organ that harbors many immune cells. For example, the hepatic Kupffer cells can produce signaling molecules in response to bacterial lipopolysaccharide and superantigens, which in turn activates the hepatic natural killer cells to produce interferon-γ [154–157].

Substantial decrease in Bifidobacterium sp., E. rectale, B. fragilis has been reported in AD [47,48]. This decrease in the number of gut commensals correlated well with cerebrospinal fluid biomarkers of AD [48].

Neural connectivity and calcium signaling defect

Neurotransmitter signaling defect influences neuronal Ca^{2+} homeostasis, which in turn affects the β-amyloid precursor protein cleavage. Recent works have shown that the gut alone produces over 60 types of neurotransmitters. Thus dysfunctions in the gut homeostasis due to abnormal gut microbiota can result to disordered synthesis of the gut neurotransmitters, which in turn can affects signaling in the gut-brain axis, Ca^{2+} signaling, subsequently leading to increased amyloid protein production [158]. But accumulation of Aβ can disrupt both peripheral and central Ca^{2+} homeostasis and render neurons susceptible to metabolic or other environmental insults or injury, consequently resulting to apoptotic cell death as seen in AD [125].

At the peripheral level (gut), Ca^{2+} homeostasis in the cell is maintained, in part, by claudins and G-protein coupled Ca^{2+} sensing receptor (CaSR) [95,159,160]. Following dysfunctions in claudin expression due to the activities of abnormal gut microbiota, claudin-CaSR signaling becomes altered resulting to Ca^{2+} singling defect that may lead to cellular toxicity. Though Ca^{2+} is a secondary messenger that is required in almost every cell for a couple of physiological processes, excessive or prolonged unregulated increase can become detrimental to the cell [92,148]. Surprisingly, the vagus nerve endings, which mediate information transfer in the microbiota-gut-brain axis, also express the CaSR. Dysfunctions of CaSR signaling in the vagus nerve have been associated with disorder in efferent electrical activity in this nerve and its integrating center and immune system dysfunctions [95,159]. These disorders can worsen the development and progression of AD. Importantly, destabilization of intracellular Ca^{2+} signaling has been implicated in neurodegeneration associated with AD [96,97,161].

Excessive or prolonged elevation of intracellular Ca^{2+} level at the peripheral and central level also activates lipases, which degrades plasma membrane proteins to generate free radicals that further cause destruction of cellular components. Sustained increase in cytosolic Ca^{2+} level can activate Ca^{2+}-dependent proteases, which may lead to hyperphosphorylation of microtubule associated proteins, triggering changes in cytoskeleton, similar to those observed in AD [96,97,148,161].

More so, disordered electrical activity in central neurons can activate the cleavage of APP resulting to the formation of sAPPβ and Aβ [97]. The secreted form of APP cleavage as well as the accumulating amyloid peptide can substantially affect neurotransmitter (e.g. glutamate, gamma-aminobutyric acid, GABA) signaling that further aggravate the effect of the disease on synaptic plasticity and development [96,148]. Relatively recent study suggests that inhibition of long term potentiation is one of the main mechanisms that mediates cognitive impairment in AD, and may be due to higher levels of GABAA receptor alpha1 subunit, NR2B subunit of the N-methyl-D-aspartate (NMDA) receptor, and postsynaptic density marker 95 (PSD-95) [162]. The aggregates of Aβ resulting to dysfunctional neurotransmitter signaling can lead to neuro- and glio-toxicity mediated by glutamate, and the kainite and NMDA receptors, among others [22,163].

Dysfunctions of gut microbiota–endocrine pathway

Endocrine connectivity is a bidirectional functional association between the gut microbiota and brain structures that allows the transfer of humoral factors, which mediate a range of brain activities including cognitive processes [164,165]. Gut derived hormones regulate energy homeostasis, and exert considerable influence on the enteric nervous system, central nervous system, modulating cognitive functions [20,166].

Growth hormones protect neurons from toxicity and excessive excitatory signaling [157], in part by stabilizing Ca^{2+} signaling, suppressing the expression of kainite, NMDA, and certain subunits of GABAA receptors in multiple brain areas. Such growth factors include but are not limited to basic fibroblast growth factor, nerve growth factor, and insulin like growth factors [148,157]. In addition, these growth factors have protective role on mitochondrial functions. This way, growth factors prevents neurodegenerative processes that characterized such disease as AD [20]. Furthermore, the gut synthesized hormones leptin, ghrelin, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide confer neuroprotective effects against toxicity induced Aβ aggregation. Reduction of the level of these gut hormones in AD has been reported. More importantly, these hormones have been shown to protect both neurons and glial cells from metabolic stress due to Aβ. Also, the gut hormones are also believed to prevent the formation of oligomers and plaques seen in AD [20]. Thus application of analogs of these hormones may

substantially cause improvement of symptoms and slow the progression of AD.

AD is also related to brain insulin signaling. Cerebral insulin signaling disorder has been reported to result from the aggregation of Aβ, possibly due to altered expression of insulin genes [166–168]. This is believed to be the underlying cause of insulin resistance in AD patients. Consequently, pharmacological development of insulin degrading enzyme and neprilysin for Aβ degradation in AD therapy may have positive results for sufferers of the disease [167,168].

Increase in toxins produced by the abnormal gut microbiota can accelerate the development or worsen the progression of Alzheimer's disease

Abnormal gut microbiota, characterized by the presence of pathogenic microbes as well as reduction in the number of beneficial microbes, results in increased production of toxic metabolites such as p-cresol sulfate, indole-3 acetic, indoxyl sulfate, trimethylamine N-oxide, phenol- and sulfur-containing compounds as well as ammonia [169–175]. Increased production of these toxins by the activities of the abnormal gut microbiota can result to disorders of metabolism and local and systemic inflammatory responses [169–171]. Furthermore, these toxins can damage the intestinal barrier and normal composition of the gut microbiota, leading to translocation of potentially pathogenic bacteria into the bloodstream [93,176]. The inflammatory responses, neurotoxicity due to the toxic metabolites can facilitate the development and progression of AD [8–10,47,48,166–168].

Decrease in metabolic products of beneficial microbiota is a critical underlying factor for the development and progression of Alzheimer's disease

The gut microbiota synthesizes several bioactive molecules, notably, folate, biotin, short chain fatty acids such as propionate, acetate and butyrate, and other bioactive molecules, which modulate both peripheral and central processes, preventing metabolic stress and other environmental insults or injury [56,177]. The gut microbiota metabolites are used locally by the epithelial cells of the gut or transported into the circulatory system to exert a plethora of effects on the host cell. The short chain fatty acids, for instance, exert their influences on the cell, at least in part, by activating the G-protein-coupled receptors, GPR41, GPR43, and GPR109 [178]. The short chain fatty acids, in particular, also exert a neuromodulatory influence on certain gut neuroendocrine cells and enterocytes, especially of the colon, which are specialized in the synthesis of incretin hormone glucagon-like peptide-1 and a couple of other gut peptides [20]. The short chain fatty acids exert antioxidant, phagocytotic, antitumorigenic, antimicrobial, chemotaxic, and anti-inflammatory influence on the gut [178]. The overall effect of adequate gut humoral signaling is to decrease the risk of development or progression of AD [20]. Thus disordered signaling of gut hormones due to the activities of abnormal gut microbiota will culminate in increased risk of development or progression of AD [9]. Therapeutic application of short chain fatty acids in AD prevention or treatment may have positive implications on the phase conversion and incidence of the disease.

The gut microbiota can shape the development and progression of Alzheimer's disease through epigenetic modifications of the host cells

The epigenetic modifications or gene signature alteration resulting from the influences of the environment or stimuli from other sources (exercise, diet, toxins) can confer behavioral features that are seen in patients with AD or other mental disorders [49,179]. Epigenetic modifications such as DNA methylation or histone modifications can affect gene expression and thus cause behavioral and cognitive changes seen in some neurological disorders [180]. These epigenetic modifications also lead to changes in second messenger signaling that compromise synaptic long-term potentiation in brain regions implicated in cognitive processing [49]. The gut microbiota can shape the host system by regulation of the epigenetic profile of the host cells. Epigenetic modification by gut microbiota can influence the development or progression of AD. Through their metabolites, the gut commensals regulate immune cell functions (e.g. cytokine synthesis). For example, short-chain fatty acids such as butyrate and propionate can promote the differentiation of naïve T cell into Treg by inhibiting histone deacetylases, a distinct class of epigenome modifying enzymes, and opposite in function to histone acetyltransferases. The histone deacetylases function by removing the acetyl group from lysine residues on cellular structures [181–183]. Metabolic pathways such as tricarboxylic acid cycle regulate epigenetic modification. The epigenetic modification "DNA methylation" is utilized by the gut microbiota to influence the host cell functions, by their regulatory influence on the enzymes that regulate this methylation, known as DNA methyltransferases [179].

Thus the gut microbiota forms a critical nexus between the gut and the host by epigenetic modification [177]. Pathogenic microbes or disordered gut microbiota affect epigenetic profile of cells *via* direct changes on the gut microbiota or indirect changes of their metabolites [177]. For instance choline- or methyl-scavenging bacteria increase susceptibility to metabolic disease (methyl groups and choline are required for epigenetic modifications) [184].

Bacteriotherapy as potential treatment option for Alzheimer's disease

Since commensal microorganisms can influence local and distant sites, there is potential positive influence on the

development or progression of AD if used as therapeutic option (Figure 5) [185,186]. The use of nutrietics or nutraceuticals (also known as psychobiotics) such as probiotics, prebiotics and synbiotics to treat cognitive and behavioral disorders has been shown to alleviate the symptoms of AD (Figure 5) [187–189]. Probiotics are live microorganisms similar to beneficial microorganisms found in the gut (e.g. *Bifidobacterium, Saccharomyces boulardii, Lactobacilli–L. acidophilus, L. casei, L. paracasei, L. zeae, L. rahmnosus, L. reuteri/ L. fermentum*) [72,73,187]. Prebiotics are the non-digestible components of food that confer substantial benefit to the host by enhancing the activities of the gut microbiota [174]. Synbiotics are a combination of both probiotics and prebiotics [174,190,191].

Psychobiotics, according to recent preclinical and clinical evidences, repress the production of neuro- and glio-toxins, and may provide an effective intervention strategy for treating neurodevelopmental and neurodegenerative diseases [84,173,174]. Psychobiotics activate metabolic, hormonal, neural pathways that prevent the detrimental effects of Aβ aggregation or prevent Aβ oligomer or plaque formation [54]. The nutrietics decrease the circulating proinflammatory cytokines and increase signaling of neuro- and glio-protective factors that prevent neurodegenerative processes. Also, nutrietics can restore disordered neuronal and glial proteolytic pathways, which are compensatory means by which brain cells prevent accumulation of toxins and apoptotic cell death [20].

There are two main types of psychobiotic therapy–oral bacteriotherapy and fecal microbiota transfer [8].

Though treatment with psychobiotics has shown to substantially increase the beneficial community of gut microbiota and improved learning and memory functions in both animal models of AD [192] and human subjects with cognitive impairment [20,89,193–195], psychobiotics such as probiotics may not always give the expected result of improving cognitive functions in AD for the following reasons. The limitation of the current available probiotics includes their use for the purpose of prophylactics in high-risk individuals. Furthermore, colonization of the gut by the components of the probiotics requires time before the benefits are realized, especially in high risk individuals. The interaction between the pathogenic gut microbiota and probiotic components may not always result to positive effects that will be observed in the individual. How the different polymorphic forms of the gut microbiota may interact with probiotic bacteria has not been fully established. Also, the expected benefits may substantially reduce due to the methods of storage or adverse effects of stomach acidity. Though microencapsulation techniques can be developed for specific strains used in probiotics to improve bacterial survival and prevent damages in adverse conditions caused by external environment. Comorbidities such as viral diseases in the gut and other illnesses can reduce the benefits of probiotics use [196].

Oral bacteriotherapy

Clinical trials have shown that ingestion of psychobiotics improves both gut and brain functions in patients with AD [84]. Therefore oral bacteriotherapy can be used in AD treatment [20].

Commensal microbiota transfer therapy

Several reports have shown that transplantation of commensal microbes into the gut reduces symptoms of gut inflammation, neurodegenerative, neurodevelopment and psychological disorders [197–199]. A recent clinical trial revealed that a high initial dose followed by a lower daily maintenance dose of microbiota transfer therapy for 8 weeks confer beneficial role on gut microbiota composition and significantly reduces of symptoms of gastrointestinal and neurological disorders [89].

Does Alzheimer's disease predispose an individual to disorders in gut microbiota?

All studies [8–10,47,48] in this review support the hypothesis that AD is associated or is caused by disordered gut microbiota, however, none has precisely reported whether or not AD directly causes disorders in gut microbiota. It is therefore imperative to investigate the influences of AD (in different disease phases) on the gut microbiota while controlling for other factors such as ageing and epigenetic modifications of the gut microbiota.

CONCLUSION

The association between gut microbiota and AD development and progression is due to multiple signaling mechanisms that involve metabolic, neuroimmune, neurohumoral pathways, modulated by

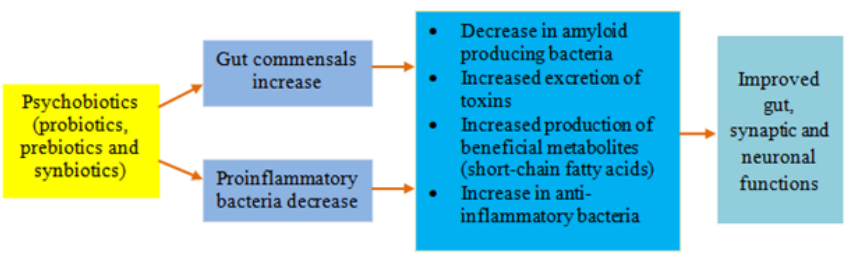

Figure 5: Multiple influences of psychobiotics

several factors. The gut microbiota has substantial role in the development and progression of AD though the microbiota-gut-brain axis which mediates a bidirectional flow of substances. This review strategically highlights potential therapeutic options for AD.

CONFLICT OF INTEREST

Author declares that there is no conflict of interest.

REFERENCES

1. Welcome MO. History of development of gastrointestinal physiology: From antiquity to modern period and the birth of modern digestive physiology, In Gastrointestinal Physiology. Springer, Cham 2018; 1-51.
2. Welcome MO, Mastorakis NE, Pereverzev VA. Neuropsychological functions of the gut microbiota, In Advances in Psychobiology. New York, USA, Nova Science Publishers 2018; 267–79.
3. König J, Wells J, Cani PD, et al. Human intestinal barrier function in health and disease. Clin Transl Gastroenterol 2016; 7:e196.
4. Bischoff SC, Barbara G, Buurman W, et al. Intestinal permeability–A new target for disease prevention and therapy. BMC Gastroenterol 2014; 14:189.
5. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J 2017; 474:1823-36.
6. Lin L, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. BMC Immunol 2017; 18:2.
7. Tremlett H, Bauer KC, Appel-Cresswell S, et al. The gut microbiome in human neurological disease: A review. Ann Neurol 2017; 81:369-82.
8. Jiang C, Li G, Huang P, et al. The gut microbiota and Alzheimer's disease. J Alzheimers Dis 2017; 58:1-5.
9. Hu X, Wang T, Jin F. Alzheimer's disease and gut microbiota. Sci China Life Sci 2016; 59:1006-23.
10. Alkasir R, Li J, Li X, et al. Human gut microbiota: The links with dementia development. Protein Cell 2017; 8:90-102.
11. De Strooper B, Vassar R, Golde T. The secretases: Enzymes with therapeutic potential in Alzheimer disease. Nat Rev Neurol 2010; 6:99.
12. De-Paula VJ, Radanovic M, Diniz BS, et al. Alzheimer's disease. Subcell Biochem 2012; 65:329-52.
13. Kowal SL, Dall TM, Chakrabarti R, et al. The current and projected economic burden of Parkinson's disease in the United States. Mov Disord 2013; 28:311-8.
14. Neugroschl J, Wang S. Alzheimer's disease: Diagnosis and treatment across the spectrum of disease severity. Mt Sinai J Med 2011; 78:596-612.
15. Chow VW, Mattson MP, Wong PC, et al. An overview of APP processing enzymes and products. Neuromolecular Med 2010; 12:1-2.
16. Kimura A, Hata S, Suzuki T. Alternative selection of β-site APP-cleaving enzyme 1 (BACE1) cleavage sites in amyloid β-protein precursor (APP) harboring protective and pathogenic mutations within the Aβ sequence. J Biol Chem 2016; 291:24041-53.
17. Yan R, Vassar R. Targeting the β secretase BACE1 for Alzheimer's disease therapy. Lancet Neurol 2014; 13:319-29.
18. Jiang L, Sui D, Qiao K, et al. Impaired functional criticality of human brain during Alzheimer's disease progression. Sci Rep 2018; 8:1324.
19. Du X, Wang X, Geng M. Alzheimer's disease hypothesis and related therapies. Transl Neurodegener 2018; 7:2.
20. Bonfili L, Cecarini V, Berardi S, et al. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. Sci Rep 2017; 7:2426.
21. Kahl A, Blanco I, Jackman K, et al. Cerebral ischemia induces the aggregation of proteins linked to neurodegenerative diseases. Sci Rep 2018; 8:2701.
22. Melkonyan MM, Hunanyan L, Lourhmati A, et al. Neuroprotective, neurogenic, and amyloid beta reducing effect of a novel alpha 2-adrenoblocker, mesedin, on astroglia and neuronal progenitors upon hypoxia and glutamate exposure. Int J Mol Sci 2017; 19:9.
23. Squire LR, Stark CE, Clark RE. The medial temporal lobe. Annu Rev Neurosci 2004; 27:279-306.
24. Kiernan JA. Anatomy of the temporal lobe. Epilepsy Res Treat 2012; 2012.
25. Fändrich M, Schmidt M, Grigorieff N. Recent progress in understanding Alzheimer's β-amyloid structures. Trends Biochem Sci 2011; 36:338-45.
26. Crews L, Masliah E. Molecular mechanisms of neurodegeneration in Alzheimer's disease. Hum Mol Genet 2010; 19:R12-20.
27. Ribarič S. Peptides as potential therapeutics for Alzheimer's disease. Molecules 2018; 23:283.
28. Declercq LD, Vandenberghe R, Van Laere K, et al. Drug development in Alzheimer's disease: The contribution of PET and SPECT. Front Pharmacol 2016; 7:88.
29. Estrada LD, Soto C. Disrupting β-amyloid aggregation for Alzheimer disease treatment. Curr Top Med Chem 2007; 7:115-26.
30. Stefanacci RG. The costs of Alzheimer's disease and the value of effective therapies. Am J Manag Care 2011; 17:S356-62.
31. Jumpertz T, Rennhack A, Ness J, et al. Presenilin is the molecular target of acidic γ-secretase modulators in living cells. PloS One 2012; 7:e30484.

32. Xu J, Wang J, Wimo A, et al. The economic burden of dementia in China, 1990–2030: Implications for health policy. Bull World Health Organ 2017; 95:18.
33. Brookmeyer R, Johnson E, Ziegler-Graham K, et al. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007; 3:186-91.
34. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement 2016; 12:292-323.
35. Hohman TJ, McLaren DG, Mormino EC, et al. Alzheimer's disease neuroimaging initiative. Asymptomatic Alzheimer disease: Defining resilience. Neurology 2016; 87:2443-50.
36. Tobias M, Yeh LC, Johnson E. Burden of Alzheimer's disease: Population-based estimates and projections for New Zealand, 2006–2031. Aust N Z J Psychiatry 2008; 42:828-36.
37. Rice DP, Fillit HM, Max W, et al. Prevalence, costs, and treatment of Alzheimer's disease and related dementia: A managed care perspective. Am J Manag Care 2001; 7:809-20.
38. Takizawa C, Thompson PL, van Walsem A, et al. Epidemiological and economic burden of Alzheimer's disease: A systematic literature review of data across Europe and the United States of America. J Alzheimers Dis 2015; 43:1271-84.
39. Chandra V, Ganguli M, Pandav R, et al. Prevalence of Alzheimer's disease and other dementias in rural India, The Indo-US study. Neurology 1998; 51:1000-8.
40. Ganguli M, Dodge HH, Chen P, et al. Ten-year incidence of dementia in a rural elderly US community population the MoVIES project. Neurology 2000; 54:1109-16.
41. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. Alzheimers Dement 2016; 12:459-509.
42. Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement 2013; 9:208-45.
43. Sadik K, Wilcock G. The increasing burden of Alzheimer disease. Alzheimer Dis Assoc Disord 2003; 17:S75-9.
44. Lopez-Bastida J, Serrano-Aguilar P, Perestelo-Perez L, et al. Social-economic costs and quality of life of Alzheimer disease in the Canary Islands, Spain. Neurology 2006; 67:2186-91.
45. Reed C, Belger M, Dell'Agnello G, et al. Caregiver burden in Alzheimer's disease: Differential associations in adult-child and spousal caregivers in the GERAS observational study. Dement Geriatr Cogn Disord Extra 2014; 4:51-64.
46. Alzheimer's A. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015; 11:332.
47. Hsiao EY, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 2013; 155:1451-63.
48. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep 2017; 7:13537.
49. Heijtz RD, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci USA 2011; 108:3047-52.
50. Welcome MO. Functional relationship between the gut and other tissues/organs of the body, In Gastrointestinal Physiology. Springer, Cham 2018; 1009-28.
51. Collado MC, Rautava S, Aakko J, et al. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. Sci Rep 2016; 6:23129.
52. Romano-Keeler J, Weitkamp JH. Maternal influences on fetal microbial colonization and immune development. Pediatr Res 2014; 77:189.
53. Wassenaar TM, Panigrahi P. Is a foetus developing in a sterile environment? Lett Appl Microbiol 2014; 59:572-9.
54. Jiménez E, Marín ML, Martín R, et al. Is meconium from healthy newborns actually sterile? Res Microbiol 2008; 159:187-93.
55. Foster JA, Neufeld KA. Gut–brain axis: How the microbiome influences anxiety and depression. Trends Neurosci 2013; 36:305-12.
56. Russo R, Cristiano C, Avagliano C, et al. Gut-brain axis: Role of lipids in the regulation of inflammation, pain and CNS diseases. Curr Med Chem 2017.
57. Clarke SF, Murphy EF, Nilaweera K, et al. The gut microbiota and its relationship to diet and obesity: New insights. Gut Microbes 2012; 3:186-202.
58. Fujio-Vejar S, Vasquez Y, Morales P, et al. The gut microbiota of healthy chilean subjects reveals a high abundance of the phylum verrucomicrobia. Front Microbiol 2017; 8:1221.
59. Bien J, Palagani V, Bozko P. The intestinal microbiota dysbiosis and Clostridium difficile infection: Is there a relationship with inflammatory bowel disease? Ther Adv Gastroenter 2013; 6:53-68.
60. Rosen CE, Palm NW. Functional classification of the gut microbiota: The key to cracking the microbiota composition code: Functional classifications of the gut microbiota reveal previously hidden contributions of indigenous gut bacteria to human health and disease. BioEssays 2017; 39:1700032.
61. Chen H, Jiang W. Application of high-throughput sequencing in understanding human oral microbiome related with health and disease. Front Microbiol 2014; 5:508.

62. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. J Bacteriol 2010; 192:5002-17.
63. Harris JK, Fang R, Wagner BD, et al. Esophageal microbiome in eosinophilic esophagitis. PLoS One 2015; 10:e0128346.
64. Liu N, Ando T, Ishiguro K, et al. Characterization of bacterial biota in the distal esophagus of Japanese patients with reflux esophagitis and Barrett's esophagus. BMC Infect Dis 2013; 13:130.
65. Baron S. Protozoa: Structure, classification, growth, and development-Medical microbiology. University of Texas Medical Branch at Galveston 1996.
66. Sekirov I, Russell SL, Antunes LC, et al. Gut microbiota in health and disease. Physiol Rev 2010; 90:859-904.
67. McLean JS. Advancements toward a systems level understanding of the human oral microbiome. Front Cell Infect Microbiol 2014; 4:98.
68. Sankar SA, Lagier JC, Pontarotti P, et al. The human gut microbiome, A taxonomic conundrum. Syst Appl Microbiol 2015; 38:276-86.
69. Rosenberg E, DeLong EF, Lory S, et al. The Prokaryotes: Gammaproteobacteria. Berlin: Springer 2014.
70. hmpdacc.org/
71. www.ncbi.nlm.nih.gov/taxonomy
72. Ribeiro AC, Matarazzo F, Faveri M, et al. Exploring bacterial diversity of endodontic microbiota by cloning and sequencing 16S rRNA. J Endod 2011; 37:922-6.
73. Eid HM, Wright ML, Anil Kumar NV, et al. Significance of microbiota in obesity and metabolic diseases and the modulatory potential by medicinal plant and food ingredients. Front Pharmacol 2017; 8:387.
74. Abbasian F, Saberbaghi T. Metagenomic study of human gastrointestinal tracts in health and diseases. J Gastroenterol Hepatol Res 2013; 2:885-96.
75. Matsumoto M, Kibe R, Ooga T, et al. Cerebral low-molecular metabolites influenced by intestinal microbiota: A pilot study. Front Syst Neurosci 2013; 7:9.
76. Jiang H, An L, Lin SM, et al. A statistical framework for accurate taxonomic assignment of metagenomic sequencing reads. PLoS One 2012; 7:e46450.
77. Hiraoka S, Yang CC, Iwasaki W. Metagenomics and bioinformatics in microbial ecology: Current status and beyond. Microbes Environ 2016; 31:204-12.
78. Sohn MB, An L, Pookhao N, et al. Accurate genome relative abundance estimation for closely related species in a metagenomic sample. BMC Bioinfo 2014; 15:242.
79. Lagier JC, Million M, Hugon P, et al. Human gut microbiota: Repertoire and variations. Front Cell Infect Microbiol 2012; 2:136.
80. Franzini PZ, Ramond JB, Scholtz CH, et al. The gut microbiomes of two Pachysoma MacLeay desert dung beetle species (Coleoptera: Scarabaeidae: Scarabaeinae) feeding on different diets. PloS One 2016; 11:e0161118.
81. Suzuki TA, Worobey M. Geographical variation of human gut microbial composition. Biol Lett 2014; 10:20131037.
82. Chen L, Zhang YH, Huang T, et al. Gene expression profiling gut microbiota in different races of humans. Sci Rep 2016; 6:23075.
83. Gupta VK, Paul S, Dutta C. Geography, ethnicity or subsistence-specific variations in human microbiome composition and diversity. Front Microbiol 2017; 8:1162.
84. Mancuso C, Santangelo R. Alzheimer's disease and gut microbiota modifications: The long way between preclinical studies and clinical evidence. Pharmacol Res 2017.
85. Hill JM, Clement C, Pogue AI, et al. Pathogenic microbes, the microbiome, and Alzheimer's disease (AD). Front Aging Neurosci 2014; 6:127.
86. Harach T, Marungruang N, Duthilleul N, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci Rep 2017; 7:41802.
87. Tsunoda I. Lymphatic system and gut microbiota affect immunopathology of neuroinflammatory diseases, including multiple sclerosis, neuromyelitis optica and Alzheimer's disease. Clin Exp Neuroimmunol 2017; 8:177-9.
88. Sampson TR, Mazmania SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe 2015; 17:565-76.
89. Kang DW, Adams JB, Gregory AC, et al. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: An open-label study. Microbiome 2017; 5:10.
90. Zhan G, Yang N, Li S, et al. Abnormal gut microbiota composition contributes to cognitive dysfunction in SAMP8 mice. Aging 2018.
91. Wu SC, Cao ZS, Chang KM, et al. Intestinal microbial dysbiosis aggravates the progression of Alzheimer's disease in Drosophila. Nat Commun 2017; 8:24.
92. Dufner MM, Kirchhoff P, Remy C, et al. The calcium-sensing receptor acts as a modulator of gastric acid secretion in freshly isolated human gastric glands. Am J Physiol Gastrointest 2005; 289:G1084-90.
93. A Kohler C, Maes M, Slyepchenko A, et al. The gut-brain axis, including the microbiome, leaky gut and bacterial translocation: Mechanisms and pathophysiological role in Alzheimer's disease. Curr Pharm Des 2016; 22:6152-66.
94. Welcome MO, Mastorakis NE. Emerging

concepts in brain glucose metabolic functions: From glucose sensing to how the sweet taste of glucose regulates its own metabolism in astrocytes and neurons. Neuromolecular Med 2018; 1-20.
95. Owen JL, Cheng SX, Ge Y, et al. The role of the calcium-sensing receptor in gastrointestinal inflammation, In Seminars in cell & developmental biology. Academic Press 2016; 49:44-51.
96. Mattson MP, Barger SW, Cheng B, et al. β-Amyloid precursor protein metabolites and loss of neuronal Ca^{2+} homeostasis in Alzheimer's disease. Trends Neurosci 1993; 16:409-14.
97. Smith-Swintosky VL, Mattson MP. Glutamate, beta-amyloid precursor proteins, and calcium mediated neurofibrillary degeneration, In Cell and Animal Models in Aging and Dementia Research. Springer, Vienna 1994; 29-45.
98. Hu C, Xu J, Zeng L, et al. Pen-2 and Presenilin are sufficient to catalyze notch processing. J Alzheimers Dis 2017; 56:1263-9.
99. Mullan M, Crawford F, Axelman K, et al. A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N–terminus of β–amyloid. Nat Genet 1992; 1:345.
100. Finckh U, Müller-Thomsen T, Mann U, et al. High prevalence of pathogenic mutations in patients with early-onset dementia detected by sequence analyses of four different genes. Am J Hum Genet 2000; 66:110-7.
101. Jonsson T, Atwal JK, Steinberg S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 2012; 488:96.
102. Kero M, Paetau A, Polvikoski T, et al. Amyloid precursor protein (APP) A673T mutation in the elderly Finnish population. Neurobiol Aging 2013; 34:1518-e1.
103. Wainaina MN, Chen Z, Zhong C. Environmental factors in the development and progression of late-onset Alzheimer's disease. Neurosci Bull 2014; 30:253-70.
104. Lahiri DK, Maloney B, Riyaz Basha M, et al. How and when environmental agents and dietary factors affect the course of Alzheimer's disease: The "LEARn" model (latent early-life associated regulation) may explain the triggering of AD. Curr Alzheimer Res 2007; 4:219-28.
105. Bertram S, Brixius K, Brinkmann C. Exercise for the diabetic brain: How physical training may help prevent dementia and Alzheimer's disease in T2DM patients. Endocrine 2016; 53:350-63.
106. Hu N, Yu JT, Tan L, et al. Nutrition and the risk of Alzheimer's disease. Biomed Res Int 2013; 2013.
107. Solfrizzi V, Panza F, Frisardi V, et al. Diet and Alzheimer's disease risk factors or prevention: The current evidence. Expert Rev Neurother 2011; 11:677-708.
108. Solfrizzi V, Capurso C, D'Introno A, et al. Lifestyle-related factors in predementia and dementia syndromes. Expert Rev Neurother 2008; 8:133-58.
109. Frisardi V, Panza F, Seripa D, et al. Nutraceutical properties of Mediterranean diet and cognitive decline: Possible underlying mechanisms. J Alzheimers Dis 2010; 22:715-40.
110. Panza F, Capurso C, D'Introno A, et al. Alcohol drinking, cognitive functions in older age, predementia, and dementia syndromes. J Alzheimers Dis 2009; 17:7-31.
111. Griswold MG, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018; 392:1015-35.
112. Welcome MO, Pereverzev VA. Glycemic allostasis during mental activities on fasting in non alcohol users and alcohol users with different durations of abstinence. Ann Med Health Sci Res 2014; 4:199-207.
113. Welcome MO, Pereverzeva EV, Pereverzev VA. A novel psychophysiological model of the effect of alcohol use on academic performance of male medical students of Belarusian State Medical University. Int J Collab Res Intern Med Public Health 2010; 2:183.
114. Welcome MO, Razvodovsky YE, Pereverzeva EV, et al. State of cognitive functions of students-medics with different relationship to alcohol use. Belarusian State Medical University Press, Minsk, Belarus 2013; 5-160.
115. Paolella G, Mandato C, Pierri L, et al. Gut-liver axis and probiotics: Their role in non-alcoholic fatty liver disease. World J Gastroenterol 2014; 20:15518.
116. Wen L, Duffy A. Factors influencing the gut microbiota, inflammation, and type 2 diabetes. J Nutr 2017; 147:1468S-75S.
117. Lima-Ojeda JM, Rupprecht R, Baghai TC. I Am I and My Bacterial Circumstances: Linking gut microbiome, neurodevelopment, and depression. Front Psychiatry. 2017; 8:153.
118. Santos CY, Snyder PJ, Wu WC, et al. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimers Dement 2017; 7:69-87.
119. Akter K, Lanza EA, Martin SA, et al. Diabetes mellitus and Alzheimer's disease: Shared pathology and treatment? Br J Clin Pharmacol 2011; 71:365-76.
120. Carlsson CM. Type 2 diabetes mellitus, dyslipidemia, and Alzheimer's disease. J Alzheimers Dis 2010; 20:711-22.
121. Zetterberg H, Mattsson N. Understanding the cause of sporadic Alzheimer's disease. Expert Rev Neurother 2014; 14:621-30.
122. Morris GP, Clark IA, Vissel B. Inconsistencies

and controversies surrounding the amyloid hypothesis of Alzheimer's disease. Acta Neuropathol Commun 2014; 2:135.
123. Thakur AK, Shakya A, Husain GM, et al. Gut-microbiota and mental health: Current and future perspectives. J Pharmacol Clin Toxicol 2014; 2:1016.
124. Dinan TG, Cryan JF. Gut instincts: Microbiota as a key regulator of brain development, ageing and neurodegeneration. J Physiol 2017; 595:489-503.
125. Cristiano C, Lama A, Lembo F, et al. Interplay between peripheral and central inflammation in autism spectrum disorders: Possible nutritional and therapeutic strategies. Front Physiol 2018; 9:184.
126. Sawada N, Murata M, Kikuchi K, et al. Tight junctions and human diseases. Med Electron Microscopy 2003; 36:147-56.
127. Förster C. Tight junctions and the modulation of barrier function in disease. Histochem Cell Biol 2008; 130:55-70.
128. Awad WA, Hess C, Hess M. Enteric pathogens and their toxin-induced disruption of the intestinal barrier through alteration of tight junctions in chickens. Toxins 2017; 9:60.
129. Zihni C, Mills C, Matter K, et al. Tight junctions: From simple barriers to multifunctional molecular gates. Nat Rev Mol Cell Biol 2016; 17:564.
130. Luettig J, Rosenthal R, Barmeyer C, et al. Claudin-2 as a mediator of leaky gut barrier during intestinal inflammation. Tissue barriers 2015; 3: e977176.
131. Welcome MO. Intercellular network of junctions of the gastrointestinal tract, In Gastrointestinal Physiology. Springer, Cham 2018; 201-25.
132. Welcome MO. Structural and functional organization of the gastrointestinal tract, In Gastrointestinal Physiology. Springer, Cham 2018; 53-106.
133. Kelly JR, Kennedy PJ, Cryan JF, et al. Breaking down the barriers: The gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci 2015; 9:392.
134. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med 2014; 6:263ra158.
135. Gonçalves A, Ambrósio AF, Fernandes R. Regulation of claudins in blood-tissue barriers under physiological and pathological states. Tissue barriers 2013; 1:e24782.
136. Capaldo CT, Powell DN, Kalman D. Layered defense: How mucus and tight junctions seal the intestinal barrier. J Mol Med 2017; 95:927-34.
137. Amasheh S, Fromm M, Günzel D. Claudins of intestine and nephron–A correlation of molecular tight junction structure and barrier function. Acta Physiol 2011; 201:133-40.
138. Welcome MO. Immunomodulatory functions of the gastrointestinal tract, In Gastrointestinal Physiology. Springer, Cham 2018; 685-771.
139. Pistollato F, Sumalla Cano S, Elio I, et al. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. Nutr Rev 2016; 74:624-34.
140. McCarthy CG, Goulopoulou S, Wenceslau CF, et al. Toll-like receptors and damage-associated molecular patterns: Novel links between inflammation and hypertension. Am J Physiol Heart Circ Physiol 2013; 306:H184-96.
141. Suresh R, Mosser DM. Pattern recognition receptors in innate immunity, host defense, and immunopathology. Adv Physiol Educ 2013; 37:284-91.
142. Thompson MR, Kaminski JJ, Kurt-Jones EA, et al. Pattern recognition receptors and the innate immune response to viral infection. Viruses 2011; 3:920-40.
143. Rouka E, Vavougios GD, Solenov EI, et al. Transcriptomic analysis of the claudin interactome in malignant pleural mesothelioma: Evaluation of the effect of disease phenotype, asbestos exposure, and CDKN2A deletion status. Front Physiol 2017; 8:156.
144. Land WG. The role of damage-associated molecular patterns (DAMPs) in human diseases: Part II: DAMPs as diagnostics, prognostics and therapeutics in clinical medicine. Sultan Qaboos Univ Med J 2015; 15:e157.
145. Afratis NA, Karamanou K, Piperigkou Z, et al. The role of heparins and nano-heparins as therapeutic tool in breast cancer. Glycoconj J 2017; 34:299-307.
146. Skandalis SS, Dobra K, Götte M, et al. Impact of extracellular matrix on cellular behavior: A source of molecular targets in disease. BioMed Res Int 2015; 2015.
147. Kim SH, Turnbull J, Guimond S. Extracellular matrix and cell signalling: The dynamic cooperation of integrin, proteoglycan and growth factor receptor. J Endocrinol 2011; 209:139-51.
148. Welcome MO. Molecular mechanisms of gastrointestinal signaling, In Gastrointestinal Physiology. Springer, Cham 2018; 227-315.
149. Kilpatrick DC, Chalmers JD. Human L-ficolin (ficolin-2) and its clinical significance. BioMed Res Int 2012; 2012.
150. Degn SE, Jensen L, Olszowski T, et al. Co-complexes of MASP-1 and MASP-2 associated with the soluble pattern-recognition molecules drive lectin pathway activation in a manner inhibitable by MAp44. J Immunol 2013; 1300780.
151. Møller-Kristensen M, Thiel S, Sjöholm A, et al. Cooperation between MASP-1 and MASP-2 in

the generation of C3 convertase through the MBL pathway. Int Immunol 2006; 19:141-9.
152. Zhang YJ, Li S, Gan RY, et al. Impacts of gut bacteria on human health and diseases. Int J Mol Sci 2015; 16:7493-519.
153. Welcome MO. Gastrointestinal physiology: Development, principles and mechanism of regulation. Springer Nature, Cham, Switzerland 2018.
154. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiol Stress 2017.
155. Dobashi H, Seki S, Habu Y, et al. Activation of mouse liver natural killer cells and NK1. 1+ T cells by bacterial superantigen-primed Kupffer cells. Hepatology 1999; 30:430-6.
156. Parker GA, Picut CA. Liver immunobiology. Toxicol Pathol 2005; 33:52-62.
157. Gao B, Radaeva S, Park O. Liver natural killer and natural killer T cells: Immunobiology and emerging roles in liver diseases. J Leukoc Biol 2009; 86:513-28.
158. Welcome MO. Neural secretions and regulation of gut functions, In Gastrointestinal Physiology. Springer, Cham 2018; 527-684.
159. Tang L, Cheng CY, Sun X, et al. The extracellular calcium-sensing receptor in the intestine: Evidence for regulation of colonic absorption, secretion, motility, and immunity. Front Physiol 2016; 7:245.
160. Riccardi D, Brown EM. Physiology and pathophysiology of the calcium-sensing receptor in the kidney. Am J Physiol Renal Physiol 2009; 298:F485-99.
161. Cheng SX, Lightfoot YL, Yang T, et al. Epithelial CaSR deficiency alters intestinal integrity and promotes proinflammatory immune responses. FEBS Lett 2014; 588:4158-66.
162. Yoshiike Y, Kimura T, Yamashita S, et al. GABAA receptor-mediated acceleration of aging-associated memory decline in APP/PS1 mice and its pharmacological treatment by picrotoxin. PloS One 2008; 3:e3029.
163. Mattson MP, Cheng B, Davis D, et al. beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. J Neurosci 1992; 12:376-89.
164. Quigley EM. Prebiotics and probiotics in digestive health. Clin Gastroenterol Hepatol 2018.
165. Clarke G, Stilling RM, Kennedy PJ, et al. Minireview: Gut microbiota: The neglected endocrine organ. Mol Endocrinol 2014; 28:1221-38.
166. Welcome MO. Gastrointestinal hormones, In Gastrointestinal Physiology, Springer Nature, Cham, Switzerland 2018; 455–526.
167. Bekkering P, Jafri I, Van Overveld FJ, et al. The intricate association between gut microbiota and development of type 1, type 2 and type 3 diabetes. Expert Rev Clin Immunol 2013; 9:1031-41.
168. Jha NK, Jha SK, Kumar D, et al. Impact of insulin degrading enzyme and neprilysin in Alzheimer's disease biology: Characterization of putative cognates for therapeutic applications. J Alzheimers Dis 2015; 48:891-917.
169. Naseer M, Bibi F, H Alqahtani M, et al. Role of gut microbiota in obesity, type 2 diabetes and Alzheimer's disease. CNS Neurol Disord Drug Targets 2014; 13:305-11.
170. Rossi M, Johnson DW, Campbell KL. The kidney–gut axis: Implications for nutrition care. J Ren Nutr 2015; 25:399-403.
171. Coppo R. The gut–kidney axis in IgA nephropathy: Role of microbiota and diet on genetic predisposition. Pediatr Nephrol 2018; 33:53-61.
172. Wing MR, Patel SS, Ramezani A, et al. Gut microbiome in chronic kidney disease. Exp Physiol 2016; 101:471-7.
173. Fernandez-Prado R, Esteras R, Perez-Gomez MV, et al. Nutrients turned into toxins: Microbiota modulation of nutrient properties in chronic kidney disease. Nutrients 2017; 9:489.
174. De Preter V, Vanhoutte T, Huys G, et al. Effect of lactulose and Saccharomyces boulardii administration on the colonic urea-nitrogen metabolism and the bifidobacteria concentration in healthy human subjects. Aliment Pharmacol Ther 200; 23:963-74.
175. vince AJ, Burridge SM. Ammonia production by intestinal bacteria: The effects of lactose, lactulose and glucose. J Med Microbiol 1980; 13:177-91.
176. Sabatino A, Regolisti G, Brusasco I, et al. Alterations of intestinal barrier and microbiota in chronic kidney disease. Nephrol Dial Transplant 2014; 30:924-33.
177. Lee ES, Song EJ, Nam YD. Dysbiosis of gut microbiome and its impact on epigenetic regulation. J Clin Epigenet 2017; 1:14.
178. Tan J, McKenzie C, Potamitis M, et al. The role of short-chain fatty acids in health and disease, In Advances in immunology. Academic Press 2014; 121:91-119.
179. Paul B, Barnes S, Demark-Wahnefried W, et al. Influences of diet and the gut microbiome on epigenetic modulation in cancer and other diseases. Clin Epigenet 2015; 7:112.
180. Alam R, Abdolmaleky HM, Zhou JR. Microbiome, inflammation, epigenetic alterations, and mental diseases. Am J Med Genet B Neuropsychiatr Genet 2017; 174:651-60.
181. Chen B, Sun L, Zhang X. Integration of microbiome and epigenome to decipher the pathogenesis of autoimmune diseases. J Autoimmun 2017; 83:31-42.
182. Alenghat T. Epigenomics and the microbiota. Toxicol Pathol 2015; 43:101-6.

183. Schilderink R, Verseijden C, de Jonge WJ. Dietary inhibitors of histone deacetylases in intestinal immunity and homeostasis. Front Immunol 2013; 4:226.
184. Romano KA, Martinez-del Campo A, Kasahara K, et al. Metabolic, epigenetic, and transgenerational effects of gut bacterial choline consumption. Cell Host Microbe 2017; 22:279-90.
185. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun 2014; 38:1-2.
186. Sherwin E, Dinan TG, Cryan JF. Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci 2018; 1420:5-25.
187. Dash S, Clarke G, Berk M, et al. The gut microbiome and diet in psychiatry: Focus on depression. Curr Opin Psychiatry 2015; 28:1-6.
188. Luna RA, Foster JA. Gut brain axis: Diet microbiota interactions and implications for modulation of anxiety and depression. Curr Opin Biotechnol 2015; 32:35-41.
189. Sherman MP, Zaghouani H, Niklas V. Gut microbiota, the immune system, and diet influence the neonatal gut–brain axis. Pediatr Res 2014; 77:127.
190. Cheng W, Lu J, Li B, et al. Effect of functional oligosaccharides and ordinary dietary fiber on intestinal microbiota diversity. Front Microbiol 2017; 8:1750.
191. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients 2017; 9:1021.
192. Wang J, Ye F, Cheng X, et al. The effects of LW-AFC on intestinal microbiome in senescence-accelerated mouse prone 8 strain, a mouse model of Alzheimer's disease. J Alzheimers Dis 2016; 53:907-19.
193. Akbari E, Asemi Z, Daneshvar Kakhaki R, et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: A randomized, double-blind and controlled trial. Front Aging Neurosci 2016; 8:256.
194. Zhao H, Shi Y, Luo X, et al. The effect of fecal microbiota transplantation on a child with tourette syndrome. Case Rep Med 2017; 2017.
195. Ceccarelli G, Brenchley JM, Cavallari EN, et al. Impact of high-dose multi-strain probiotic supplementation on neurocognitive performance and central nervous system immune activation of HIV-1 infected individuals. Nutrients 2017; 9:1269.
196. Evivie SE, Huo GC, Igene JO, et al. Some current applications, limitations and future perspectives of lactic acid bacteria as probiotics. Food Nutr Res 2017; 61:1318034.
197. Ruggiero M. Fecal microbiota transplantation and the brain microbiota in neurological diseases. Clin Endosc 2016; 49:579.
198. König J, Siebenhaar A, Högenauer C, et al. Consensus report: Faecal microbiota transfer–Clinical applications and procedures. Aliment Pharmacol Ther 2017; 45:222-39.
199. Li Q, Han Y, Dy AB, et al. The gut microbiota and autism spectrum disorders. Front Cell Neurosci 2017; 11:120.