

Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications

Mak Adam Daulatzai*

Sleep Disorders Group, EEE/MSE, The University of Melbourne, Grattan Street, Parkville, Victoria 3010, Australia

Abstract

Obesity, an epidemic problem in the world is associated with several health problems. An understanding of mechanisms/factors that predispose, delay or protect individuals from obesity and its associated metabolic disturbances and cognitive impairment would be invaluable. The human gut harbors a diverse population of microbial organisms which are symbiotic and important for well being. However, studies on conventional and germ-free animals have shown that alteration in normal commensal gut microbiota and an increase in pathogenic microbiome (termed "dysbiosis") contribute to gut inflammation, generation of LPS and pro-inflammatory cytokines, gut leakage, and systemic- and neuro-inflammation. The immune mechanisms that are necessary for gut homeostasis may become dysfunctional and lead to bowel inflammation and gut-brain axis dysfunction. These factors are potentially involved in inducing obesity as well. It may be wise to consider the wider hypothesis that gut's dysbiosis, commencing as a response to fatty food, modulates neuro-inflammation and cognitive dysfunction. This may be enhanced by concomitant noxious factors such as consumption of NSAIDs and alcohol in the elderly. The neurotoxic mechanisms when chronic may enhance vulnerability to dementia of Alzheimer's type (AD), and perhaps contribute to other dementias as well. Therapeutic strategies for amelioration of cognitive decline and AD are desperately needed. It is pragmatic then that immunologically mediated gut dyshomeostasis is abrogated by available options including Prebiotics, Probiotics, and Synbiotics. Decreasing gut's dysbiosis may thus attenuate neuroinflammation and provide a potential treatment for obesity-related cognitive impairment. Further, the 'gut-brain axis' or 'brain-gut axis' (depending on whether one considers bottom-up or top-down pathway) is a bi-directional communication system, comprised of neural pathways encompassing enteric nervous system and the vagus. Vagus nerve stimulation in conjunction with $\alpha 7$ nAChR agonists may be an important therapeutic modality in gut pathology to upregulate parasympathetic/vagal efferent function, ameliorate gut-brain axis dysfunction and neuroinflammation, and decrease vulnerability to AD.

Keywords: Obesity; Dysbiosis; Endotoxemia; Neuroinflammation; Hippocampus; Cognitive impairment

Introduction

Obesity is an epidemic problem in the world. Since obesity is associated with an increased risk for heart disease, stroke, type 2 diabetes, several comorbidities, and early death, it places an enormous burden on health-care services. As per World Health Organization (WHO) estimation, 1.5 billion adults aged 20 years and older were overweight in 2008; over 200 million men and 300 million women — approximately 10% of adults were obese. The National Heart, Lung, and Blood Institute and the WHO define overweight as a BMI equal to or greater than 25 kg/m² and obese as a BMI equal to or greater than 30 kg/m² [1,2]. As of 2009, the estimated figures of the Centers for Disease Control reveal that a staggering 49 U.S. states have a prevalence of obesity of 20% or greater and 9 states have a prevalence of over 30%. Although obesity accounts for an estimated 400,000 deaths each year [3], it is also a leading preventable cause of death.

The decline in life expectancy due to obesity has been extensively studied [4,5]; it is largely attributable to the many health consequences of obesity, such as cardiovascular disease, type 2 diabetes, sleep apnea, and cancer [6]. Obese adults have been shown to be 5 times more likely to have high blood pressure (BP) and 40 times more likely to have type 2 diabetes (DM) than the normal weight persons [7-10].

As well as the above co-morbidities, obesity is also associated with poor neurocognitive outcome. There is accumulating evidence that an elevated BMI is linked to higher risk of Alzheimer's disease (AD) due to increased structural brain changes, including white matter alteration,

and excess age-related brain atrophy [11-16]. Various cross-sectional studies find that excess weight is also associated with reduced cognitive function [17-22]. Consistent with these findings, longitudinal data from the Framingham Heart Study have also shown that obesity is indeed associated with accelerated cognitive decline in aging [23, 24]. Recently, the Whitehall II Cohort Study documented that long-term obesity in adulthood is associated with lower cognition in late midlife. In analyses adjusted for age, sex, and education, being obese at 2 or 3 occasions in lifespan was associated with lower Mini-Mental State Examination scores and scores of memory and executive function [25].

The gut microbial ecology and the physiological impacts of gut microbial communities in human/animal hosts have become the focus of intense research in recent years. There is bidirectional communication between the host and gut-resident microbiota, referred

*Corresponding author: Mak Adam Daulatzai, M.Sc., Ph.D., M.D., Ph.D, Senior Medical Research Fellow, Sleep Disorders Group, EEE Dept, Melbourne School of Engineering, The University of Melbourne, 3rd Floor, Room No. 344, Parkville, Victoria 3010, Australia, Tel: +613 834 48830; Fax: +613 934 71094; E-mail : mak@drmakdaulatzai.us Or makd@unimelb.edu.au

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to as inter-kingdom signaling [26-28]. This mediates the symbiotic and pathogenic relationships between the gut bacteria and mammalian hosts. Commensal microbiota interacts with the intestinal mucosa and influences the amplitude of the immune response and thus activity of the immune system. In contrast, host gut can influence microbes, which in turn modulate disease susceptibility. Indeed, dysregulated host-microbial interactions can result in intestinal inflammation and cause physiological dyshomeostasis in the host.

We now appreciate that the etiology of many human diseases involves both genetic and environmental factors. Indeed, the incidence of several human diseases, including obesity, diabetes and atherosclerosis, has strong environmental contribution. The reciprocal nature of the regulation of the immune system and gut microbiota is at the core - in terms of dysfunctions involved in the pathogenesis of obesity and obesity-related disorders [29-34]. This paper deals with alterations in gut microbiota - i.e. dysbiosis, gut inflammation, enhanced generation of lipopolysaccharide (LPS), increased intestinal permeability, metabolic endotoxemia, and development of obesity, causing metabolic dyshomeostasis and cognitive dysfunction/AD. Further, it has implications for understanding gut-brain axis dysfunction owing to gut microbiota-obesity-related dysregulated pathophysiological mechanisms, and for utilizing pragmatic therapeutic strategies for attenuating this disease condition and ameliorating cognitive decline.

Obesity

Results from a significant amount of literature have advanced our understanding of obesity. For example, studies in humans have put forth the mechanisms through which we now appreciate the relationship between gut microbiota and obesity [35]. With steady rise in the prevalence of obesity worldwide and its associated diseases, it is essential that we gain understanding of the mechanisms that dysregulate body's energy homeostasis and the pathology that promotes cognitive dysfunction in humans [36]. There is significant literature emphasizing that the hippocampus plays a pivotal role in obesity-associated cognitive dysfunction.

Adipose tissue is not only a storage depot of fat but is also the largest endocrine organ in the human/animal body that secretes hormones, cytokines, and growth factors [37-39]. To date, more than 50 different molecular entities have been discovered released from the adipose tissue; these are generally referred to as 'adipokines'. The wide range of molecular entities includes leptin, adiponectin, TNF- α , IL-1 β , IL-6, IL-10, monocyte chemoattractant protein-1, macrophage migration inhibitory factor, NGF, vascular endothelial growth factor, plasminogen activator inhibitor 1, and haptoglobin. In addition to the above mentioned, the list further includes transforming growth factor- β (TGF β), chemokines (IL-8), monocyte chemoattractant protein-1 (MCP-1), and macrophage migration inhibitory factor β (MIF β), acute phase proteins (AI-1), haptoglobin, serum amyloid A (SAA), and angiogenic factors (VEGF) [37].

A link between obesity and AD has been emphasized [36,40]. Metabolic syndrome (MetS) is associated with neurocognitive impairments, owing to a long-term effect of poor metabolism. However, even relatively short-term impairments in metabolism, without clinically manifest vascular disease, may be associated with smaller hippocampal volumes and cognitive decline [41]. Western high-energy diet intake (i.e. consumption of high saturated fats and high simple carbohydrates, HFHS) is associated with cognitive impairment and hippocampal-dependent memory inhibition [42]. Rats that consumed this diet had poor hippocampal-dependent cognitive

functioning. Further, diets rich in HFHS showed deleterious effect on BBB permeability [43] and reduced BDNF in the hippocampus [44,45].

Aging and Inflammation Upregulation

Immunosenescence - i.e. deterioration of the immune system with age is associated with an increased susceptibility to infection and autoimmune disease among others. Indeed, normal ageing is considered to be a chronic low-grade pro-inflammatory state that may have up to a 4-fold increase in serum levels of pro-inflammatory mediators. LPS-stimulated macrophages from 65-yr-old subjects generated significantly more IL-1, TNF- α , and IL-6, and significantly more exosomal mRNAs for TNF- α , IL-6, and IL-12, than macrophages from 21- to 45-yr-old subjects [46,47]. Systemic inflammation markers including C-reactive protein (CRP), TNF- α , IL-1 β , IL-6, IL-8, IL-10, IL-12, plasminogen activator inhibitor, SAA, and vascular adhesion molecule-1 were analyzed (controlling for age, sex, education, cardiovascular risk factors, obesity and other metabolic factors, smoking, alcohol consumption, depression and presence of the apolipoprotein ϵ 4 genotype) in 873 non-demented community-dwelling elderly participants, aged 70-90 years [47]. Cytokines, e.g. IL-6 and IL-12 were associated with reduced speed and executive processing functions in the the Sydney Memory and Ageing Study [48].

A variety of factors may contribute to the inflammatory state including the recurring and/or chronic antigenic stress that may affects immune system activating macrophages and related cells [46,49]. Aging also has an effect on the stability of gut microbial communities. Aging is associated with reduced immune function; however, increased use of medications, alcohol, and changes in nutrition—all of which may modify the gut microbiota [49]. Further, there is increased production of pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, and IL-8 in the elderly [47]. Other data have confirmed the above mentioned as well as documented NF-kappaB, cyclooxygenase-2, adhesion molecules, and inducible NO synthase as other key players involved in the age-related Upregulation of inflammatory process [51,52]. LPS stimulation elicited higher cytokine and exosomal mRNA (ex-mRNA) responses from CNS-located macrophages (CM) in older subjects. A β - and LPS-stimulated CMs from 65-yr-old subjects that generated significantly more TNF- α , IL-1 β , and IL-6, and significantly more ex-mRNAs for TNF- α , IL-6, and IL-12, than CMs from 20 matched 21- to 45-yr-old subjects [46].

Gut Microbiota and Energy Harvesting

Diet is one of the most important determinants of microbial diversity within the gut [53]. There are significant shifts in gut microbiome composition according to differing diets [54,55]. The gut microbiota is an important environmental factor and has a regulatory function on energy metabolism of the host [56] via energy harvest from the diet and energy storage in the host [57-60]. The Western-type diet i.e. high-fat, high-sugar (HFHS), or high polysaccharide-containing plant diets have been shown to significantly alter gut's microbiome composition [61,62]. This is reflected by the fact that despite feeding a high-fat diet, the microbiota of both rats [63] and mice [64] when enriched in Clostridiales in the Firmicutes phylum, do not become obese. Furthermore, subjects who achieved weight loss demonstrated increased counts of *Bacteroides fragilis* and *Lactobacillus* and decreased counts of *Clostridium coccoides* and *Bifidobacterium longum* [65]. There is evidence that germ-free mice are protected against obesity; however, the transfer of gut microbiota from conventionally raised animal to germ-free animal results in dramatic increase in body fat

content of the latter [58]. Indeed, the pathogenesis of obesity is a function of the impact of diet on the gut microbiome owing in part to the differing composition of the latter existing between lean and obese humans and mice [55].

Obesity and Cerebrovascular changes

Obesity exerts several negative effects on the brain. For example, obesity and its associated risk factors have an impact on the cerebral vasculature. Indeed, pathological alterations in the cerebral vasculature correlated with an increased blood pressure (BP) which may be an essential contributor to brain pathology in the obese rats and human population [66,67]. The middle cerebral arteries of obese Zucker rats (OZR) undergo structural remodeling and they have greater cerebral injury after cerebral ischemia. Such cerebrovascular changes correlate with the development of hypertension which is the major determinant for stroke risk in obese subjects [68]. Mean gray matter cerebral blood flow (CBF) was found to be 15% lower in individuals with metabolic syndrome (MetS) compared to controls. Voxel-wise image analysis indicated that the MetS subjects possess lower CBF across a large portion of the cortex. Those with MetS show lower immediate memory function; a mediation analysis indicated this relationship in part to be mediated by CBF. Abdominal obesity and elevated triglycerides (among the MetS factors) were most strongly associated with lower CBF in metabolic syndrome patients [69]. This highlights the importance of reducing the cardiovascular risk factors in order to maintain CBF and cognition in an aging obese population.

Importantly, it has been demonstrated that obesity is tightly correlated with higher level of reactive oxygen species (ROS), which in the brain promotes cognitive impairment [70]. Owing to significant impairment in glutathione peroxidase, there is a direct relationship between obesity and the level of oxidative stress within the brain [70]. Consequently, in the metabolically abnormal obese with oxidative stress, the decline on the global score was found to be faster than among normal weight individuals [71]. Further, it has been documented recently that aging exacerbates obesity-induced oxidative stress and inflammation in peri-vascular adipose tissue in mice [48]. In view of the abovementioned modulating factors in obesity, it is not surprising that clinically MetS subjects are considered to have an elevated risk of vascular dementia [72,73].

Gut inflammation, LPS Leakage and Obesity

Inflammation is a coordinated response to noxious stimuli, in order to maintain homeostasis. The obesity-triggered inflammatory response involves many components of the classical inflammatory pathway that includes systemic hyper-cytokemia, acute phase proteins (e.g. CRP), and recruitment of leukocytes to the gut and adipose tissue (i.e. the inflamed tissues) and activation of tissue leukocytes plus generation of LPS in humans [74,75]. LPS – an endotoxin is derived from the cell wall of gram-negative bacteria; it circulates at low concentrations in the blood of healthy individuals. However, in the presence of high fat (HF) diet-induced obesity there is a substantial increase in gut pathogenic microbiome and metabolic endotoxemia i.e. when LPS concentration is much higher in the blood in both animals and humans [76,77].

Bacteria and HF diet interact to promote pro-inflammatory changes in the gut which has a strong and significant association with progression of obesity [78-80]. Rodent and human studies demonstrate that chronic inflammation is characterized by macrophage infiltration in adipose tissue during obesity [81,82]. There is increased TNF- α secretion from hypertrophied adipocytes [83]. This condition

causes alteration of the immune cells, including TH1 cells, B cells, neutrophils, and mast cells that induce M1 activation of macrophages owing to elevated levels of TNF- α and IFN γ . Further, the secretion of chemoattractants such as MCP-1 and MIF and of cytokines TNF- α , IL-1 β , and IL-6, drive immune cells including dendritic cells, T cells, and macrophages into adipose tissue. Thus, this may develop a feedback loop of pro-inflammatory cytokines that exacerbates inflammatory pathology, and causes further immune cell infiltration and enhanced cytokine secretion in both animals and humans [84]. This promotes an ongoing upregulation of the inflammatory milieu.

To recapitulate, consumption of a HF diet by both animals and humans results in changes to the gut microbiota composition (see above), and significant increases in LPS/endotoxin concentrations [85,86]. The systemic LPS/endotoxin level from pathogenic microbiota results from increased intestinal permeability. This sequence of events is evidenced by the study in which antibiotics were administered to both HF-fed and *ob/ob* mice [87]. This treatment resulted in reduced levels of gut LPS content, endotoxemia, intestinal permeability, body weight gain and fat mass deposition, markers of inflammation, oxidative stress, and infiltration of macrophages into visceral adipose tissue. Thus, the gut microbiota in conjunction with HF diet, are pivotal in influence the development of chronic low-level systemic inflammation and obesity.

Comments

Neuroinflammation

During the past decade, it has been demonstrated that persistent excess of nutritional intake and over-nutrition-induced obesity result in chronic and low-grade inflammation. This leads to up-regulation of IKK β /NF- κ B-induced neuroinflammation. The neuroinflammation impairs central regulatory pathways of energy balance and nutritional metabolism, thus leading to obesity, diabetes, cardiovascular, and other complications [81,88-91]. Hypothalamic inflammation can impair insulin release from β cells, impair peripheral insulin action, and potentiate hypertension, as revealed in rodents [92-94]. Many of these effects are generated by signals from the sympathetic nervous system, which is also capable of inducing inflammatory changes in adipose tissue in response to neuronal injury [95].

Adipose tissue and brain from HF diet-fed animals show increased TNF- α as well as macrophage and microglial activation. Further, both brains and adipose tissue may also show elevated amyloid precursor protein (APP) levels localized to neurons, macrophage and adipocytes [81]. Thus, as documented in a murine model of high fat diet-induced obesity, the latter may result in concomitant pro-inflammatory changes in brain and adipose tissue; however, the increased level of APP may be a further contributing factor to upregulate inflammatory changes [81].

Neuroinflammation is associated with a variety of neurodegenerative diseases including AD. Old age is associated with innate peripheral immune stimulation (see above) and an increase in neuroinflammation [96-104]. LPS has been shown to increase inflammatory response in the brain of healthy aged mice [105]. When young and old mice were injected with *Escherichia coli* LPS to mimic an acute peripheral infection/endotoxemia, the hippocampus of old animals had an increased inflammatory response, compared to younger animals [106]. Following LPS injection, mRNA encoding TNF- α , IL-1 β , and IL-6 was higher in hippocampal neurons of old mice compared to their young counterparts [106]. The hippocampus of LPS-treated old mice had more microglial cells; moreover, IL-1 β -positive cells were present

in the dentate gyrus (DG) and in the CA1, CA2, and CA3, compared to young adults [106,107]. In a test of cognition (to integrate new information and complete a spatial task in a mouse model of working memory version - water maze), the hippocampal processing was found dysfunctional in LPS-treated old animals compared to the younger ones [106]. This is due in part to compromised hippocampal neurogenesis and impaired hippocampus-dependent spatial memory as confirmed recently in the LPS-induced inflammatory paradigm [108]. The above data on infection-related cognitive impairment is consistent with studies showing a link between aging, endotoxemia, and deterioration of the hippocampus cells [109], resulting in hippocampal dysfunction and cognitive decline [110,111]. There is an inherent relationship between infection and cognition, in that infection in the elderly induces cognitive impairment, while cognitive dysfunction exacerbates infection [107,112,113]. An analogous situation would be - obesity enhances gut's pathogenic bacteria, while the latter upregulate systemic endotoxemia which in turn causes neuroinflammation and cognitive decline, as per animals and human studies [96-111].

An elegant study utilized a transgenic mouse model whose unique feature involved human IL-1 β transgene that directed overexpression of IL-1 β , with temporal and regional control [114]. The human IL-1 β overexpression activated glia, enhanced IL-1 β protein and PGE-2 levels, and elevated pro-inflammatory cytokine and chemokine mRNAs - all specifically within the hippocampus. IL-1 β overexpression for two weeks attenuated hippocampus-dependent long-term contextual and spatial memory in mice, while hippocampus-independent short-term memory lacked any detectable loss. IL-1 β -associated neuroinflammation also reduced levels of the plasticity-related gene *Arc* [114]. Chronic systemic inflammation has been shown to induce proinflammatory microglial phenotype in middle-aged rats. Further, microglia expresses IL-1 β in the hippocampal CA1 region of rats in an age-dependent manner also. Inflammation induces deficits in the LTP in the Schaffer collateral-CA1 synapses of the older rats (but not in young animals), and impairs post-tetanic potentiations in the hippocampus [115].

Impact of obesity on the hippocampus

Obesity - a growing global health problem not only contributes to diabetes, hypertension, cardiovascular diseases, and cancer, but it may also cause dementia. Obesity is considered to be a risk factor for AD and vascular dementia being associated with neuroinflammation and impaired cognitive function. The hippocampus is sensitive to inflammatory insults and subjects with peripheral/systemic infections may manifest cognitive dysfunction [106,107,116,117]. This is because the inflammatory cytokines have confirmed impaired synaptic plasticity in the DG and CA regions of the animal hippocampus [118-123].

The identification of neurodegenerative changes in obese Zucker rats (OZR) may represent important features for better characterizing neuronal involvement in this model of MetS. Both pre-frontal cortex (PFC) and hippocampus showed an increased number of GFAP immunoreactive astrocytes; they were located in the CA1 and CA3 subfields and dentate gyrus of OZR (compared to their lean rats) [124].

The increased consumption of saturated fats in a HF diet (HFD) contributes to obesity, memory loss, and cognitive impairment in C57BL/6 mice [125]. HFD increased the toxic level of malondialdehyde, reduced the growth of neural progenitor cells, and decreased the level of brain-derived neurotrophic factor (BDNF) in the hippocampus. The impairment affecting the hippocampal neurogenesis was ascribed to increased lipid peroxidation and decreased BDNF [125].

In an interesting study, high fat refined carbohydrate diet (HF/RC) has been shown to alter recruitment of transcription factors and decreases CREB phosphorylation, possibly due to oxidative-related pathways [126]. This is also considered to modulate the vulnerability of the hippocampal CA1 region to the episodic hypoxia in OSA patients, thus enhancing neurocognitive decline [126].

It is important to underscore that the hippocampus is strongly linked to food-related behavior also [127,128]. It has a major function in the control of feeding behavior based on the detection and integration of energy state signals via memory and encoding information about food experiences, as shown in rodents [129]. The hippocampal-dependent memory inhibition, therefore, may be critical to refrain from responding to environmental cues associated with food, and thus consume energy intake in excess [42]. Thus, a dysfunctional hippocampus may indeed be a risk factor in obesity; obese persons would have a lower activation of the hippocampus than non-obese in response to food cues. Indeed, neuroimaging studies have shown significantly less hippocampal activation in obese subjects in response to food cues [130,131].

Gut-brain axis

The gastrointestinal tract (GIT) epithelium is constantly exposed to microbes, other pathogens, and food antigens. GIT is endowed with immunologic and non-immunologic mechanisms that neutralize and eliminate the above deleterious agents. This is accomplished by the GIT due to an extensive integrated neuro-immune network and immune system encompassing immune cells, lymphoid aggregates and intra-epithelial lymphocytes. Further, the intestinal mucosa of an adult contains about 80% of the body's activated B cells - terminally differentiated to plasma cells (PCs). Most mucosal PCs produce IgA, hence, GIT possesses abundant mucosal immunity. Further, specific receptors for neurotransmitters, such as substance P, vasoactive intestinal polypeptide (VIP), and somatostatin, are present on many immune cells. The secretion of mucus, gastric acid, water and electrolyte as well as peristalsis is regulated by gut's "intrinsic" enteric nervous system (ENS) and "extrinsic" - i.e. CNS counterparts.

Almost every GIT function is under the regulatory influence of the nervous system, including the vagal afferents, spinal afferents, sympathetic and parasympathetic efferents and the enteric nervous system (ENS). The ENS is considered to be the Gut's brain and governs the GIT activity/homeostasis. Various noxious inputs (mediating pathological symptoms) from the gut to the brain reflect processing of afferent signals [132-134]. Autonomic dysfunction/imbalance and increased sympathetic activity may impart low vagal tone; this may underpin symptomatology and alter visceral perception in gut pathology, as in functional gastrointestinal disorders, for example [135]. It is generally accepted now that there is dysfunctional bidirectional "brain-gut axis" pathway between the GIT and the CNS in patients of some gut conditions [136-139]. The symbiotic relationship between the commensal gut microbiota and its host (animals/humans) protects from the effects of infection and inflammation, and modulates the normal behavioral responses [140]. However, dysbiosis renders individuals with enhanced perception of gut stimuli, pathological symptoms (e.g. diarrhea, altered transport of intestinal gas, bowel distention, abdominal discomfort, pain, bloating) including psychosocial [141].

Consistent robust evidence indicates that pathogenic gut bacteria influence the ENS, via afferent signaling of LPS and pro-inflammatory cytokines to the brain. Various regions in the brain may then synthesize their own pro-inflammatory cytokines documented in rats [142]. Thus,

dysbiosis i.e. changes in the composition of the gut microbiota may impact normal gut physiology promoting conditions ranging from gut inflammation → to endotoxemia → to neuroinflammation → to obesity, via immune, endocrine, and neural pathways. Consequently, disturbances of the ANS occurring in obesity and other conditions such as irritable bowel syndrome may correlate with brain-gut axis dysfunction [138,143-145]. Consequently, the vagus nerve occupies an essential role subserving important communicating signals from gut bacteria/ GIT to the CNS [146,147].

Perspective on Therapeutic Strategies and Future Directions

Benefit of prebiotics, probiotics, and synbiotics

Gut microbiota—arguably the highest density of microorganisms resides in the host. Several converging studies on the GIT inflammatory conditions suggest that these conditions are probably caused by defects in host immunity due to dysbiosis. Simply put, the immune mechanisms that are necessary for gut homeostasis may become dysfunctional and lead to bowel inflammation.

It is quite pragmatic then that immunologically mediated alterations including an increase in LPS, pro-inflammatory cytokines, and gut permeability be controlled by available options. These include Prebiotics, Probiotics, and Synbiotics. Bran is an example of prebiotic; it promotes the growth of commensal bacteria e.g. *Lactobacilli* and *Bifidobacteria*. Probiotics utilize these beneficial species as exogenous supplementation to intestinal microbiota. Synbiotics are exogenous supplementation to intestinal and colonic microbiota, and exploit the synergistic benefit by combining a prebiotic with probiotic. An example would be *Bifidobacteria* plus fructooligosaccharides (or galactooligosaccharides), or *Lactobacillus rhamnosus* GG plus inulins. These ameliorate mucosal permeability and immune activation in human subjects [148], and thus minimize systemic inflammation and consequent neuroinflammation via the vagus nerve, shown in mice [149].

Further, Chronic treatment with *L. rhamnosus* (JB-1) resulted in reduced stress-induced anxiety- and depression-related behavior, as well as alterations in GABA (B1b) receptor mRNA in the mouse brain [150]. These behavioral and neurochemical ameliorating effects, however, were absent in vagotomized mice. This emphasized that the vagus is a major modulatory communication pathway between the gut microbiota and the brain. This also underscores the pivotal role of GI bacteria in the bidirectional communication of the gut-brain axis highlighting that certain gut bacterial types may indeed induce therapeutic benefits in more ways than one [149].

Vagus nerve stimulation (VNS) and $\alpha 7$ nAChR agonists

There have been considerable advances in clinical neurostimulation in recent years. VNS has been approved by the FDA as a neurostimulation modality in clinical medicine, and is not a novel treatment modality any longer. VNS is now a well-established beneficial therapy in a subset of patients with treatment-resistant depression [150] and epilepsy [151].

The current research on VNS shows that the vagus/brainstem may modulate immune responses. A recent study determined the beneficial effects of VNS in attenuating LPS-induced (intraperitoneally injected) acute lung injury (ALI) in rats. VNS improved lung injury evidenced by a significant reduction in lung edema, neutrophil infiltration, and pulmonary permeability [152]. Additionally, VNS decreased the expressions of Src-suppressed C kinase substrate and E-selectin proteins in lung tissue and effectively attenuated the levels of proinflammatory

cytokines including TNF- α , IL-1 β , and IL-6 in bronchoalveolar lavage fluid [152].

In canines with heart failure (HF), long-term, low level VNS improved left ventricular (LV) systolic function, prevented progressive LV hypertrophy, and improved biomarkers of HF (compared with control animals that did not receive VNS) [153]. Further, other studies in canine HF have also shown that Chronic VNS improves cardiac autonomic control and significantly attenuates HF [154]. The therapeutic benefit of VNS in dogs included pronounced cardiac and anti-inflammatory benefits; it improved heart rate variability and baroreflex sensitivity, and lowered plasma norepinephrine, angiotensin II, and CRP levels [154].

The effect of VNS was recently examined in LPS-challenged (intraperitoneal injection) mice. The endotoxin induced intestinal tight junction injury with increased intestinal permeability, evidenced by increased amount of fluorescein isothiocyanate-dextran (FID) in circulation [155]. VNS (of right cervical vagus nerve) [156] ameliorated the tight junction damage, decreased permeability to FID, and reversed the decreased expression of tight junction proteins occludin and zonula occludens 1 [155]. α -bungarotoxin is a specific $\alpha 7$ -nAChR antagonist, its administration prior to VNS significantly abolished the above protective impact of VNS. This study showed that attenuation of tight junction disruption and intestinal epithelial permeability in LPS-induced endotoxemia is mediated by $\alpha 7$ -nAChR [155]. The recent simplified transcutaneous auricular VNS technique may be worth pursuing since it is a simpler and least invasive VNS treatment option [157]. Given the above mentioned documented benefits of VNS on many inflammatory mechanisms in vagus-innervated organs including GIT, there is a strong case for its utilization in ameliorating obesity-related gut inflammation, systemic inflammation, neuroinflammation, and cognitive decline.

Future research on the connection between the brain and the immune system in dysfunctional gut disorders may offer Challenges and opportunities. There has been considerable emphasis on the afferent and efferent parasympathetic activity playing a crucial role in immunomodulation [140,158-161]. When mice receive LPS endotoxin, they up-regulate synthesis of proinflammatory cytokines [162,163], and there is intestinal epithelial cell shedding [164], analogous to humans. VNS has been shown to significantly inhibit TNF- α in animal receiving LPS [165]. The mechanism responsible for inhibition of cytokine synthesis is attributed to acetylcholine (ACh), which is the neurotransmitter of vagus nerve [162,163,166]. Cytokine-producing cells express $\alpha 7$ nAChR which transduce an intracellular signal that inhibits cytokine synthesis [163,166]. Moreover, VNS in $\alpha 7$ nAChR-knockout animals fails to suppress cytokine synthesis whereas it significantly inhibits cytokine release in wild-type littermates [163]. This indicates that vagus cholinergic signals in conjunction with $\alpha 7$ nAChR modulate cytokine synthesis. Hence, VNS and administration of $\alpha 7$ nAChR agonists in obesity may inhibit proinflammatory cytokines, including TNF- α , IL-1 β , and IL-6 [166-168]. Such therapeutic application may represent a novel form of treatment in patients with obesity, gut inflammatory processes, and disruption of vagal afferent and efferent functions (viz. gut-brain axis). Finally, $\alpha 7$ nAChR agonism may also have clinical benefit in ameliorating cognitive/memory dysfunction, and vulnerability to AD via attenuating tau hyperphosphorylation [169].

Conclusions

Obesity - a major public health issue promotes disability, and is

causally related to several chronic disorders shortening life span. The biology of obesity is complex. However, simply put, obesity develops from a prolonged imbalance of energy intake, energy expenditure, and energy storage. Owing to recent research we now have an ever-increasing understanding of important concepts e.g. the impact of composition and function of the gut microbiota on obesity. Under certain conditions of metabolic dysfunction - as in obesity, components of the innate immune system may be activated (in the absence of external pathogens) leading to pathologic consequences. In obesity, the latter involves LPS generation in the gut, gut leakiness to LPS, and systemic inflammation leading to neuroinflammation. Persistent systemic inflammation triggers and sustains neuroinflammation. The latter targets several brain regions including the hippocampus causing up-regulation of amyloid beta and neurofibrillary tangles, synapse/neuronal degeneration, gray matter volume atrophy, and progressive cognitive decline.

The current article highlights an up-regulated cascade in which gut-microbiota-related dysbiosis generates LPS; this then enhances a web of interactions that induce stress, depression, and cognitive decline. The ongoing neurotoxicity in obesity increases neuronal dysfunction/apoptosis in different brain regions including the hippocampus, and promotes learning and memory impairment, thus accelerating vulnerability to cognitive decline. The failure of recent clinical trials in AD is due in part to a lack of appreciation of this complex multifactorial neurotoxic-pathophysiological labyrinth, encompassing pivotal body systems such as respiratory, cardiovascular, and indeed gastrointestinal. The key in the amelioration of cognitive dysfunction is first to employ appropriate preventive strategies prior to significant hippocampus damage and memory dysfunction. Recommendation is made for such strategies, including vagus nerve stimulation.

Systemic inflammation occurs due to LPS efflux from the gut; this up-regulates neuroinflammation- including that in the hippocampus and cerebellum. Brain pro-inflammatory cytokine generation/synthesis, i.e. neuroinflammation promotes amyloid deposition and tau hyperphosphorylation that enhance hypofunction/dysfunction in key brain regions, including the hippocampus and cerebellum. This cascade of events promotes neuronal injury/apoptosis and degeneration, leading to cognitive impairment and vulnerability to Alzheimer's dementia (Figure 1).

Review Criteria

This Review article was based on searches of the PubMed database using the following terms: "Obesity", "pathogenic gut microbiota", "lipopolysaccharide", "gut inflammation", "barrier dysfunction", "systemic inflammation", "neuroinflammation", and gut-brain axis - alone and in combination. Only articles published in English were retrieved. Full-text papers were available for most of the articles, and the references of these articles were searched for further relevant material. The review is comprised of nine structured sections, plus introduction that analyze the current evidence related to obesity-related gut dysbiosis and gut inflammation, in the context of neuroinflammation. These sections evaluate the relationship of the obesity-gut microbiota to systemic and neuroinflammation - at the clinical and epidemiological, the neuroanatomical and pathophysiological levels, with reference to lipopolysaccharide, pro-inflammatory cytokines, and gut-brain-gut axis dysfunction. In the Discussion section, a conceptual framework is presented regarding the interface of obesity, dysbiosis, and gut inflammation and dysfunction, followed by a discussion of the hippocampal and cerebellar inflammation/dysfunction. Here,

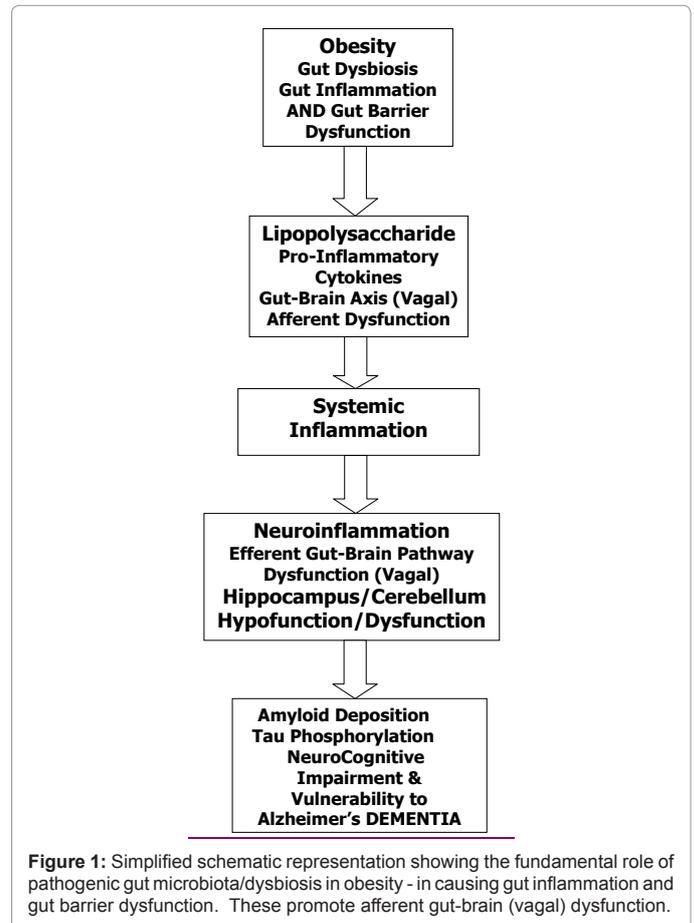


Figure 1: Simplified schematic representation showing the fundamental role of pathogenic gut microbiota/dysbiosis in obesity - in causing gut inflammation and gut barrier dysfunction. These promote afferent gut-brain (vagal) dysfunction.

significance and therapeutic efficacy is also emphasized in terms of clinical utility of probiotics, prebiotics, and synbiotics in conjunction with VNS and $\alpha 7$ nAChR agonists, to ameliorate gut inflammation, systemic inflammation, and neuro-inflammation. It is hypothesized that targeting gut-brain-gut vagal pathways could be a novel therapy for ameliorating gut inflammation, neuro-inflammation, and cognitive decline. These future directions are considered to be of potential value for they may attenuate vulnerability to AD.

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