Journal of Molecular and Genetic Medicine

ISSN: 1747-0862

Daulatzai, J Mol Genet Med 2014, S1
DOI: 10.4172/1747-0862.S1-005

Review Article Open Access

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 α7 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/m^2 and obese as a BMI equal to or greater than 30 kg/m^2 [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

Received November 11, 2013; **Accepted** December 10, 2013; **Published** December 16, 2013

Citation: Daulatzai MA (2014) Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications. J Mol Genet Med S1: 005. doi: 10.4172/1747-0862.S1-005

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 micobiota-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 secrets 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-1β, IL-6, IL-10, monocyte chemotactic 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 (TGFβ), chemokines (IL-8), monocyte chemotactic protein-1 (MCP-1), and macrophage migration inhibitory factor β (MIFβ), 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 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-1β, 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 ε4 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-inflammaory cytokines such as TNF-α, IL-1β, 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. Aβ- 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 (OZRs) 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-cytokinemia, 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 IFNγ. Further, the secretion of chemoattractants such as MCP-1 and MIF and of cytokines TNF-α, IL-1β, 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 IKKβ/NF-κB-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 results 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-1β, 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-1β-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-1β transgene that directed overexpression of IL-1β, with temporal and regional control [114]. The human IL-1β overexpression activated glia, enhanced IL-1beta protein and PGE-2 levels, and elevated pro-inflammatory cytokine and chemokine mRNAs – all specifically within the hippocampus. IL-1β 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-1β-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-1β 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 (OZRs) 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 OZRs (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 *Lactobacilis rhamnosuss* 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 α7 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-1β, 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 α7-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 α7-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 α7 nAChR which transduce an intracellular signal that inhibits cytokine synthesis [163,166]. Moreover, VNS in α7 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 α7 nAChR modulate cytokine synthesis. Hence, VNS and administration of α7 nAChR agonists in obesity may inhibit proinflammatory cytokines, including TNF- α, IL-1β, 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, alpha7 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).

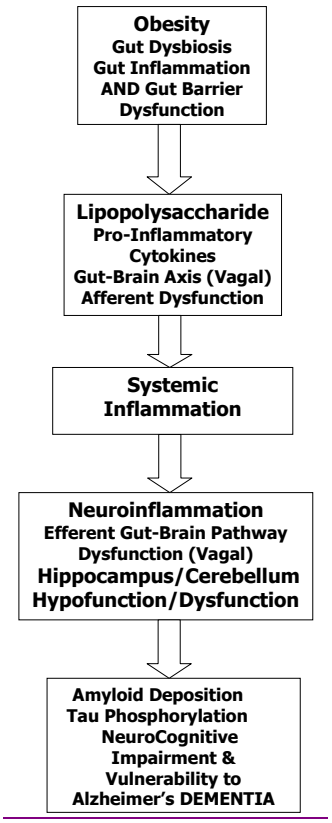

Figure 1: Simplified schematic representation showing the fundamental role of pathogenic gut microbiota/dysbiosis in obesity - in causing gut inflammation and gut barrier dysfunction. These promote afferent gut-brain (vagal) dysfunction.

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, significance and therapeutic efficacy is also emphasized in terms of clinical utility of probiotics, prebiotics, and synbiotics in conjunction with VNS and α7 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.

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR (2010) Prevalence and trends in obesity among US adults, 1999-2008. JAMA 303: 235-241.
2. [No authors listed] (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 894: i-xii, 1-253.
3. Mokdad AH, Marks JS, Stroup DF, Gerberding JL (2004) Actual causes of death in the United States, 2000. JAMA 291: 1238-1245.
4. Flegal KM, Graubard BI, Williamson DF, Gail MH (2005) Excess deaths associated with underweight, overweight, and obesity. JAMA 293: 1861-1867.
5. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, et al. (2005) A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 352: 1138-1145.
6. Bray GA (2004) Medical consequences of obesity. J Clin Endocrinol Metab 89: 2583-2589.
7. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1994) Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 17: 961-969.
8. Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, et al. (1990)

Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 132: 501-513.

9. Harris MM, Stevens J, Thomas N, Schreiner P, Folsom AR (2000) Associations of fat distribution and obesity with hypertension in a bi-ethnic population: the ARIC study. Atherosclerosis Risk in Communities Study. Obes Res 8: 516-524.
10. Rosenberg L, Palmer JR, Adams-Campbell LL, Rao RS (1999) Obesity and hypertension among college-educated black women in the United States. J Hum Hypertens 13: 237-241.
11. Gustafson D, Lissner L, Bengtsson C, Björkelund C, Skoog I (2004) A 24-year follow-up of body mass index and cerebral atrophy. Neurology 63: 1876-1881.
12. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I (2003) An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 163: 1524-1528.
13. Gustafson DR, Steen B, Skoog I (2004) Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. Int Psychogeriatr 16: 327-336.
14. Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC (2005) The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol 5: 23.
15. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, et al. (2005) Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 62: 1556-1560.
16. Jagust W, Harvey D, Mungas D, Haan M (2005) Central obesity and the aging brain. Arch Neurol 62: 1545-1548.
17. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, et al. (2007) Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr Psychiatry 48: 57-61.
18. Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E (2006) Obesity is associated with memory deficits in young and middle-aged adults. Eat Weight Disord 11: e15-19.
19. Jeong SK, Nam HS, Son MH, Son EJ, Cho KH (2005) Interactive effect of obesity indexes on cognition. Dement Geriatr Cogn Disord 19: 91-96.
20. Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, et al. (2006) Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the Advanced Cognitive Training for Independent and Vital Elderly cohort. J Am Geriatr Soc 54: 97-103.
21. Waldstein SR, Katzel LI (2006) Interactive relations of central versus total obesity and blood pressure to cognitive function. Int J Obes (Lond) 30: 201-207.
22. Cournot M, Marquié JC, Ansiau D, Martinaud C, Fonds H, et al. (2006) Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology 67: 1208-1214.
23. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB (2003) Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int J Obes Relat Metab Disord 27: 260-268.
24. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB (2005) Obesity, diabetes and cognitive deficit: The Framingham Heart Study. Neurobiol Aging 26 Suppl 1: 11-16.
25. Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A (2009) Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. Am J Clin Nutr 89: 601-607.
26. Hughes DT, Sperandio V (2008) Inter-kingdom signalling: communication between bacteria and their hosts. Nat Rev Microbiol 6: 111-120.
27. Kendall MM, Rasko DA, Sperandio V (2007) Global effects of the cell-to-cell signaling molecules autoinducer-2, autoinducer-3, and epinephrine in a luxS mutant of enterohemorrhagic Escherichia coli. Infect Immun 75: 4875-4884.
28. Pacheco AR, Sperandio V (2009) Inter-kingdom signaling: chemical language between bacteria and host. Curr Opin Microbiol 12: 192-198.
29. Garrett WS, Gordon JI, Glimcher LH (2010) Homeostasis and inflammation in the intestine. Cell 140: 859-870.
30. Musso G, Gambino R, Cassader M (2010) Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes Care 33: 2277-2284.
31. Esteve E, Ricart W, Fernández-Real JM (2011) Gut microbiota interactions with obesity, insulin resistance and type 2 diabetes: did gut microbiote co-evolve with insulin resistance? Curr Opin Clin Nutr Metab Care 14: 483-490.
32. Diamant M, Blaak EE, de Vos WM (2011) Do nutrient-gut-microbiota interactions play a role in human obesity, insulin resistance and type 2 diabetes? Obes Rev 12: 272-281.
33. Kim KA, Gu W, Lee IA, Joh EH, Kim DH (2012) High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. PLoS One 7: e47713.
34. Lam YY, Ha CW, Campbell CR, Mitchell AJ, Dinudom A, et al. (2012) Increased gut permeability and microbiota change associate with mesenteric fat inflammation and metabolic dysfunction in diet-induced obese mice. PLoS One 7: e34233.
35. Angelakis E, Armougom F, Million M, Raoult D (2012) The relationship between gut microbiota and weight gain in humans. Future Microbiol 7: 91-109.
36. Businaro R, Ippoliti F, Ricci S, Canitano N, Fuso A (2012) Alzheimer's disease promotion by obesity: induced mechanisms-molecular links and perspectives. Curr Gerontol Geriatr Res 2012: 986823.
37. Rajala MW, Scherer PE (2003) Minireview: The adipocyte--at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology 144: 3765-3773.
38. Trayhurn P, Wood IS (2005) Signalling role of adipose tissue: adipokines and inflammation in obesity. Biochem Soc Trans 33: 1078-1081.
39. Gustafson D (2006) Adiposity indices and dementia. Lancet Neurol 5: 713-720.
40. Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, et al. (2010) Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. Ageing Res Rev 9: 399-417.
41. Yau PL, Castro MG, Tagani A, Tsui WH, Convit A (2012) Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics 130: e856-864.
42. Kanoski SE, Davidson TL (2011) Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. Physiol Behav 103: 59-68.
43. Davidson TL, Monnot A, Neal AU, Martin AA, Horton JJ, et al. (2012) The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats. Physiol Behav 107: 26-33.
44. Kanoski SE, Meisel RL, Mullins AJ, Davidson TL (2007) The effects of energy-rich diets on discrimination reversal learning and on BDNF in the hippocampus and prefrontal cortex of the rat. Behav Brain Res 182: 57-66.
45. Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann RS, et al. (2008) Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus 18: 1085-1088.
46. Mitsuhashi M, Taub DD, Kapogiannis D, Eitan E, Zukley L, et al. (2013) Aging enhances release of exosomal cytokine mRNAs by Aî²1-42-stimulated macrophages. FASEB J 27: 5141-5150.
47. Rink L, Seyfarth M (1997) [Characteristics of immunologic test values in the elderly]. Z Gerontol Geriatr 30: 220-225.
48. Trollor JN, Smith E, Agars E, Kuan SA, Baune BT, et al. (2012) The association between systemic inflammation and cognitive performance in the elderly: the Sydney Memory and Ageing Study. Age (Dordr) 34: 1295-1308.
49. Bailey-Downs LC, Tucsek Z, Toth P, Sosnowska D, Gautam T, et al. (2013) Aging exacerbates obesity-induced oxidative stress and inflammation in perivascular adipose tissue in mice: a paracrine mechanism contributing to vascular redox dysregulation and inflammation. J Gerontol A Biol Sci Med Sci 68: 780-792.
50. Tiihonen K, Ouwehand AC, Rautonen N (2010) Human intestinal microbiota and healthy ageing. Ageing Res Rev 9: 107-116.
51. Chung HY, Sung B, Jung KJ, Zou Y, Yu BP (2006) The molecular inflammatory process in aging. Antioxid Redox Signal 8: 572-581.
52. Chung HY, Lee EK, Choi YJ, Kim JM, Kim DH, et al. (2011) Molecular inflammation as an underlying mechanism of the aging process and age-related diseases. J Dent Res 90: 830-840.
53. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, et al. (2006) Factors

influencing the composition of the intestinal microbiota in early infancy. Pediatrics 118: 511-521.

54. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, et al. (2010) Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A 107: 14691-14696.

55. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI (2008) Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe 3: 213-223.

56. Krajmalnik-Brown R, Ilhan ZE, Kang DW, DiBaise JK (2012) Effects of gut microbes on nutrient absorption and energy regulation. Nutr Clin Pract 27: 201-214.

57. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, et al. (2004) The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A 101: 15718-15723.

58. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, et al. (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444: 1027-1031.

59. Murphy EF, Cotter PD, Healy S, Marques TM, O'Sullivan O, et al. (2010) Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. Gut 59: 1635-1642.

60. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, et al. (2011) Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr 94: 58-65.

61. Serino M, Luche E, Gres S, Baylac A, Bergé M, et al. (2012) Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. Gut 61: 543-553.

62. Fava F, Gitau R, Griffin BA, Gibson GR, Tuohy KM, et al. (2013) The type and quantity of dietary fat and carbohydrate alter faecal microbiome and short-chain fatty acid excretion in a metabolic syndrome 'at-risk' population. Int J Obes (Lond) 37: 216-223.

63. de La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, et al. (2010) Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am J Physiol Gastrointest Liver Physiol 299: G440-448.

64. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, et al. (2009) High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology 137: 1716-1724.

65. Santacruz A, Marcos A, Wärnberg J, Martí A, Martin-Matillas M, et al. (2009) Interplay between weight loss and gut microbiota composition in overweight adolescents. Obesity (Silver Spring) 17: 1906-1915.

66. Schreihofer AM, Mandel DA, Mobley SC, Stepp DW (2007) Impairment of sympathetic baroreceptor reflexes in obese Zucker rats. Am J Physiol Heart Circ Physiol 293: H2543-2549.

67. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, et al. (2008) Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 117: e25-146.

68. Osmond JM, Mintz JD, Dalton B, Stepp DW (2009) Obesity increases blood pressure, cerebral vascular remodeling, and severity of stroke in the Zucker rat. Hypertension 53: 381-386.

69. Birdsill AC, Carlsson CM, Willette AA, Okonkwo OC, Johnson SC, et al. (2013) Low cerebral blood flow is associated with lower memory function in metabolic syndrome. Obesity (Silver Spring) 21: 1313-1320.

70. Freeman LR, Zhang L, Nair A, Dasuri K, Francis J, et al. (2013) Obesity increases cerebrocortical reactive oxygen species and impairs brain function. Free Radic Biol Med 56: 226-233.

71. Singh-Manoux A, Czernichow S, Elbaz A, Dugravot A, Sabia S, et al. (2012) Obesity phenotypes in midlife and cognition in early old age: the Whitehall II cohort study. Neurology 79: 755-762.

72. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, et al. (2010) Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. J Neurol Neurosurg Psychiatry 81: 433-440.

73. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, et al. (2011) Metabolic syndrome, mild cognitive impairment, and progression to dementia. The Italian Longitudinal Study on Aging. Neurobiol Aging 32: 1932-1941.

74. Spencer M, Yao-Borengasser A, Unal R, Rasouli N, Gurley CM, et al. (2010) Adipose tissue macrophages in insulin-resistant subjects are associated with collagen VI and fibrosis and demonstrate alternative activation. Am J Physiol Endocrinol Metab 299: E1016-1027.

75. Lumeng CN, Saltiel AR (2011) Inflammatory links between obesity and metabolic disease. J Clin Invest 121: 2111-2117.

76. Moreira AP, Texeira TF, Ferreira AB, Peluzio Mdo C, Alfenas Rde C (2012) Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. Br J Nutr 108: 801-809.

77. Brun P, Castagliuolo I, Di Leo V, Buda A, Pinzani M, et al. (2007) Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 292: G518-525.

78. Cani PD, Delzenne NM (2010) Involvement of the gut microbiota in the development of low grade inflammation associated with obesity: focus on this neglected partner. Acta Gastroenterol Belg 73: 267-269.

79. Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock NM, et al. (2010) High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. PLoS One 5: e12191.

80. Ding S, Lund PK (2011) Role of intestinal inflammation as an early event in obesity and insulin resistance. Curr Opin Clin Nutr Metab Care 14: 328-333.

81. Puig KL, Floden AM, Adhikari R, Golovko MY, Combs CK (2012) Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. PLoS One 7: e30378.

82. Zhang L, Dasuri K, Fernandez-Kim SO, Bruce-Keller AJ, Freeman LR, et al. (2013) Prolonged diet induced obesity has minimal effects towards brain pathology in mouse model of cerebral amyloid angiopathy: implications for studying obesity-brain interactions in mice. Biochim Biophys Acta 1832: 1456-1462.

83. Tateya S, Kim F, Tamori Y (2013) Recent advances in obesity-induced inflammation and insulin resistance. Front Endocrinol (Lausanne) 4: 93.

84. McArdle MA, Finucane OM, Connaughton RM, McMorrow AM, Roche HM (2013) Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. Front Endocrinol (Lausanne) 4: 52.

85. Erridge C, Attina T, Spickett CM, Webb DJ (2007) A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. Am J Clin Nutr 86: 1286-1292.

86. Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, et al. (2008) Energy intake is associated with endotoxemia in apparently healthy men. Am J Clin Nutr 87: 1219-1223.

87. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, et al. (2008) Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes 57: 1470-1481.

88. Purkayastha S, Cai D (2013) Disruption of neurogenesis by hypothalamic inflammation in obesity or aging. Rev Endocr Metab Disord 14: 351-356.

89. Cai D (2013) Neuroinflammation in overnutrition-induced diseases. Vitam Horm 91: 195-218.

90. Cai D (2013) Neuroinflammation and neurodegeneration in overnutrition-induced diseases. Trends Endocrinol Metab 24: 40-47.

91. Shefer G, Marcus Y, Stern N (2013) Is obesity a brain disease? Neurosci Biobehav Rev.

92. Kang YM, Ma Y, Zheng JP, Elks C, Sriramula S, et al. (2009) Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. Cardiovasc Res 82: 503-512.

93. Calegari VC, Torsoni AS, Vanzela EC, Araújo EP, Morari J, et al. (2011) Inflammation of the hypothalamus leads to defective pancreatic islet function. J Biol Chem 286: 12870-12880.

94. Purkayastha S, Zhang H, Zhang G, Ahmed Z, Wang Y, et al. (2011) Neural dysregulation of peripheral insulin action and blood pressure by brain endoplasmic reticulum stress. Proc Natl Acad Sci USA 108: 2939-2944.

95. Wang YY, Lin SY, Chuang YH, Chen CJ, Tung KC, et al. (2011) Adipose proinflammatory cytokine expression through sympathetic system is associated

with hyperglycemia and insulin resistance in a rat ischemic stroke model. Am J Physiol Endocrinol Metab 300: E155–E163.

96. Ye SM, Johnson RW (2001) Regulation of interleukin-6 gene expression in brain of aged mice by nuclear factor kappaB. J Neuroimmunol 117: 87-96.

97. Lee CK, Weindruch R, Prolla TA (2000) Gene-expression profile of the ageing brain in mice. Nat Genet 25: 294-297.

98. Richwine AF, Godbout JP, Berg BM, Chen J, Escobar J, et al. (2005) Improved psychomotor performance in aged mice fed diet high in antioxidants is associated with reduced *ex vivo* brain interleukin-6 production. Brain Behav Immun 19: 512-520.

99. Daulatzai MA (2012) Memory and Cognitive Dysfunctions in Alzheimer's disease are Inextricably Intertwined with Neuroinflammation due to Aging, Obesity, Obstructive Sleep Apnea, and other Upstream Risk Factors. In: Horizons in Neuroscience Research". Andres Costa and Eugenio Villalba (eds), Nova Science Publishers Inc., NY. pp 69-106.

100. Daulatzai MA (2012) Pathogenesis of cognitive dysfunction in patients with obstructive sleep apnea: a hypothesis with emphasis on the nucleus tractus solitarius. Sleep Disord 2012: 251096.

101. Daulatzai MA (2012) Dysfunctional nucleus tractus solitarius: its crucial role in promoting neuropathogenetic cascade of Alzheimer's dementia--a novel hypothesis. Neurochem Res 37: 846-868.

102. Daulatzai MA (2012) Quintessential risk factors: their role in promoting cognitive dysfunction and Alzheimer's disease. Neurochem Res 37: 2627-2658.

103. Daulatzai MA (2013) Death by a thousand cuts in Alzheimer's disease: hypoxia--the prodrome. Neurotox Res 24: 216-243.

104. Daulatzai MA (2013) Neurotoxic saboteurs: straws that break the hippo's (hippocampus) back drive cognitive impairment and Alzheimer's Disease. Neurotox Res 24: 407-459.

105. Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, et al. (2005) Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. FASEB J 19: 1329-1331.

106. Chen J, Buchanan JB, Sparkman NL, Godbout JP, Freund GG, et al. (2008) Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral innate immune system. Brain Behav Immun 22: 301-311.

107. Barrientos RM, Higgins EA, Biedenkapp JC, Sprunger DB, Wright-Hardesty KJ, et al. (2006) Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol Aging 27: 723-732.

108. Ormerod BK, Hanft SJ, Asokan A, Haditsch U, Lee SW, et al. (2013) PPARÎ³ activation prevents impairments in spatial memory and neurogenesis following transient illness. Brain Behav Immun 29: 28-38.

109. Abe Y, Toyosawa K (1999) Age-related changes in rat hippocampal theta rhythms: a difference between type 1 and type 2 theta. J Vet Med Sci 61: 543-548.

110. Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99: 195-231.

111. Avital A, Goshen I, Kamsler A, Segal M, Iverfeldt K, et al. (2003) Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus 13: 826-834.

112. Chapman TR, Barrientos RM, Ahrendsen JT, Maier SF, Patterson SL (2010) Synaptic correlates of increased cognitive vulnerability with aging: peripheral immune challenge and aging interact to disrupt theta-burst late-phase long-term potentiation in hippocampal area CA1. J Neurosci 30: 7598-7603.

113. Guerra C, Linde-Zwirble WT, Wunsch H (2012) Risk factors for dementia after critical illness in elderly medicare beneficiaries. Crit Care 16: R233.

114. Hein AM, Stasko MR, Matousek SB, Scott-McKean JJ, Maier SF, et al. (2010) Sustained hippocampal IL-1beta overexpression impairs contextual and spatial memory in transgenic mice. Brain Behav Immun 24: 243-253.

115. Liu X, Wu Z, Hayashi Y, Nakanishi H (2012) Age-dependent neuroinflammatory responses and deficits in long-term potentiation in the hippocampus during systemic inflammation. Neuroscience 216: 133-142.

116. Wofford JL, Loehr LR, Schwartz E (1996) Acute cognitive impairment in elderly ED patients: etiologies and outcomes. Am J Emerg Med 14: 649-653.

117. Chiovenda P, Vincentelli GM, Alegiani F (2002) Cognitive impairment in elderly ED patients: need for multidimensional assessment for better management after discharge. Am J Emerg Med 20: 332-335.

118. Bellinger FP, Madamba S, Siggins GR (1993) Interleukin 1 beta inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. Brain Res 628: 227-234.

119. Hellstrom IC, Danik M, Luheshi GN, Williams S (2005) Chronic LPS exposure produces changes in intrinsic membrane properties and a sustained IL-beta-dependent increase in GABAergic inhibition in hippocampal CA1 pyramidal neurons. Hippocampus 15: 656-664.

120. Rosi S, Ramirez-Amaya V, Vazdarjanova A, Worley PF, Barnes CA, et al. (2005) Neuroinflammation alters the hippocampal pattern of behaviorally induced Arc expression. J Neurosci 25: 723-731.

121. Rosi S, Pert CB, Ruff MR, McGann-Gramling K, Wenk GL (2005) Chemokine receptor 5 antagonist D-Ala-peptide T-amide reduces microglia and astrocyte activation within the hippocampus in a neuroinflammatory rat model of Alzheimer's disease. Neuroscience 134: 671-676.

122. Pickering M, O'Connor JJ (2007) Pro-inflammatory cytokines and their effects in the dentate gyrus. Prog Brain Res 163: 339-354.

123. Shaw KN, Commins S, O'Mara SM (2005) Cyclooxygenase inhibition attenuates endotoxin-induced spatial learning deficits, but not an endotoxin-induced blockade of long-term potentiation. Brain Res 1038: 231-237.

124. Tomassoni D, Nwankwo IE, Gabrielli MG, Bhatt S, Muhammad AB, et al. (2013) Astrogliosis in the brain of obese Zucker rat: a model of metabolic syndrome. Neurosci Lett 543: 136-141.

125. Park HR, Park M, Choi J, Park KY, Chung HY, et al. (2010) A hi A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. Neurosci Lett 482: 235-239.

126. Goldbart AD, Row BW, Kheirandish-Gozal L, Cheng Y, Brittian KR, et al. (2006) High fat/refined carbohydrate diet enhances the susceptibility to spatial learning deficits in rats exposed to intermittent hypoxia. Brain Res 1090: 190-196.

127. Flaherty CF, Coppotelli C, Hsu D, Otto T (1998) Excitotoxic lesions of the hippocampus disrupt runway but not consummatory contrast. Behav Brain Res 93: 1-9.

128. Jarrard LE (1973) The hippocampus and motivation. Psychol Bull 79: 1-12.

129. Davidson TL, Jarrard LE (1993) A role for hippocampus in the utilization of hunger signals. Behav Neural Biol 59: 167-171.

130. Tataranni PA, DelParigi A (2003) Functional neuroimaging: a new generation of human brain studies in obesity research. Obes Rev 4: 229-238.

131. DelParigi A, Chen K, Salbe AD, Hill JO, Wing RR, et al. (2004) Persistence of abnormal neural responses to a meal in postobese individuals. Int J Obes Relat Metab Disord 28: 370-377.

132. Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, et al. (2011) The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterol Motil 23: 1132-1139.

133. Ibeakanma C, Ochoa-Cortes F, Miranda-Morales M, McDonald T, Spreadbury I, et al. (2011) Brain-gut interactions increase peripheral nociceptive signaling in mice with postinfectious irritable bowel syndrome. Gastroenterology 141: 2098-2108.

134. Tougas G (1999) The autonomic nervous system in functional bowel disorders. Can J Gastroenterol 13 Suppl A: 15A-17A.

135. Mertz HR (2003) Overview of functional gastrointestinal disorders: dysfunction of the brain-gut axis. Gastroenterol Clin North Am 32: 463-476, v.

136. Mulak A, Bonaz B (2004) Irritable bowel syndrome: a model of the brain-gut interactions. Med Sci Monit 10: RA55-62.

137. Crowell MD, Harris L, Jones MP, Chang L (2005) New insights into the pathophysiology of irritable bowel syndrome: implications for future treatments. Curr Gastroenterol Rep 7: 272-279.

138. Hughes PA, Zola H, Penttila IA, Blackshaw LA, Andrews JM, et al. (2013) Immune activation in irritable bowel syndrome: can neuroimmune interactions explain symptoms? Am J Gastroenterol 108: 1066-1074.

139. Piche T, Barbara G, Aubert P, Bruley des Varannes S, Dainese R, et al. (2009)

Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. Gut 58: 196-201.

140. Sternberg EM (2006) Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol 6: 318-328.

141. Kerckhoffs AP, Akkermans LM, de Smet MB, Besselink MG, Hietbrink F, et al. (2010) Intestinal permeability in irritable bowel syndrome patients: effects of NSAIDs. Dig Dis Sci 55: 716-723.

142. Hosoi T, Okuma Y, Nomura Y (2000) Electrical stimulation of afferent vagus nerve induces IL-1beta expression in the brain and activates HPA axis. Am J Physiol Regul Integr Comp Physiol 279: R141-147.

143. Maier SF, Goehler LE, Fleshner M, Watkins LR (1998) The role of the vagus nerve in cytokine-to-brain communication. Ann N Y Acad Sci 840: 289-300.

144. Collins SM, Denou E, Verdu EF, Bercik P (2009) The putative role of the intestinal microbiota in the irritable bowel syndrome. Dig Liver Dis 41: 850-853.

145. Ducrotté P (2009) [Irritable bowel syndrome: from the gut to the brain-gut]. Gastroenterol Clin Biol 33: 703-712.

146. Cryan JF, Dinan TG (2012) Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 13: 701-712.

147. Forsythe P, Kunze WA (2013) Voices from within: gut microbes and the CNS. Cell Mol Life Sci 70: 55-69.

148. Barbara G, Zecchi L, Barbaro R, Cremon C, Bellacosa L, et al. (2012) Mucosal permeability and immune activation as potential therapeutic targets of probiotics in irritable bowel syndrome. J Clin Gastroenterol 46 Suppl: S52-55.

149. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, et al. (2011) Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A 108: 16050-16055.

150. Christmas D, Steele JD, Tolomeo S, Eljamel MS, Matthews K (2013) Vagus nerve stimulation for chronic major depressive disorder: 12-month outcomes in highly treatment-refractory patients. J Affect Disord 150: 1221-1225.

151. Marras CE, Chiesa V, De Benedictis A, Franzini A, Rizzi M, et al. (2013) Vagus nerve stimulation in refractory epilepsy: new indications and outcome assessment. Epilepsy Behav 28: 374-378.

152. Chen C, Zhang Y, Du Z, Zhang M, Niu L, et al. (2013) Vagal efferent fiber stimulation ameliorates pulmonary microvascular endothelial cell injury by downregulating inflammatory responses. Inflammation 36: 1567-1575.

153. Hamann JJ, Ruble SB, Stolen C, Wang M, Gupta RC, et al. (2013) Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. Eur J Heart Fail 15: 1319-1326.

154. Zhang Y, Popovic ZB, Bibevski S, Fakhry I, Sica DA, et al. (2009) Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. Circ Heart Fail 2: 692-699.

155. Zhou H, Liang H, Li ZF, Xiang H, Liu W, et al. (2013) Vagus Nerve Stimulation Attenuates Intestinal Epithelial Tight Junctions Disruption in Endotoxemic Mice Through α7-Nicotinic Acetylcholine Receptors. Shock 40: 144-151.

156. Zhang Y, Ilsar I, Sabbah HN, Ben David T, Mazgalev TN (2009) Relationship between right cervical vagus nerve stimulation and atrial fibrillation inducibility: therapeutic intensities do not increase arrhythmogenesis. Heart Rhythm 6: 244-250.

157. He W, Jing X, Wang X, Rong P, Li L, et al. (2013) Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: a pilot trial. Epilepsy Behav 28: 343-346.

158. Tracey KJ (2002) The inflammatory reflex. Nature 420: 853-859.

159. Tracey KJ (2007) Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 117: 289-296.

160. Tracey KJ (2009) Reflex control of immunity. Nat Rev Immunol 9: 418-428.

161. Van Der Zanden EP, Boeckxstaens GE, de Jonge WJ (2009) The vagus nerve as a modulator of intestinal inflammation. Neurogastroenterol Motil 21: 6-17.

162. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, et al. (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 405: 458-462.

163. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, et al. (2003) Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 421: 384-388.

164. Williams JM, Duckworth CA, Watson AJ, Frey MR, Miguel JC, et al. (2013) A mouse model of pathological small intestinal epithelial cell apoptosis and shedding induced by systemic administration of lipopolysaccharide. Dis Model Mech 6: 1388-1399.

165. van Westerloo DJ, Giebelen IA, Meijers JC, Daalhuisen J, de Vos AF, et al. (2006) Vagus nerve stimulation inhibits activation of coagulation and fibrinolysis during endotoxemia in rats. J Thromb Haemost 4: 1997-2002.

166. Wang H, Liao H, Ochani M, Justiniani M, Lin X, et al. (2004) Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. Nat Med 10: 1216-1221.

167. Jonnala RR, Buccafusco JJ (2001) Relationship between the increased cell surface alpha7 nicotinic receptor expression and neuroprotection induced by several nicotinic receptor agonists. J Neurosci Res 66: 565-572.

168. The F, Cailotto C, van der Vliet J, de Jonge WJ, Bennink RJ, et al. (2011) Central activation of the cholinergic anti-inflammatory pathway reduces surgical inflammation in experimental post-operative ileus. Br J Pharmacol 163: 1007-1016.

169. Bitner RS, Nikkel AL, Markosyan S, Otte S, Puttfarcken P, et al. (2009) Selective alpha7 nicotinic acetylcholine receptor activation regulates glycogen synthase kinase3beta and decreases tau phosphorylation in vivo. Brain Res 1265: 65-74.

This article was originally published in a special issue, **Molecular & Cellular Aspects in Obesity & Diabetes** handled by Editor(s). Dr. Masayoshi Yamaguchi, Emory University School of Medicine, USA