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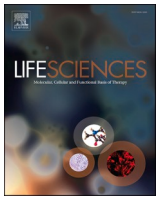

The impact of lipopolysaccharide on cerebrovascular function and cognition resulting from obesity-induced gut dysbiosis

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ABSTRACT

Obesity is a worldwide epidemic coinciding with a concomitant increase in the incidence of neurodegenerative diseases, particularly dementia. Obesity is characterised by increased adiposity, chronic low-grade systemic inflammation, and oxidative stress, which promote endothelial dysfunction. Endothelial dysfunction reduces cerebrovascular function leading to reduced cerebral blood flow and, eventually, cognitive decline, thus predisposing to a neurodegenerative disease. Obesity is also characterised by gut dysbiosis and a subsequent increase in the lipopolysaccharide which increasingly activates toll-like receptor 4 (TLR4) and further promotes chronic low-grade systemic inflammation. This also disrupts the crosstalk within the gut-brain axis, thus influencing the functions of the central nervous system, including cognition. However, the mechanisms by which obesity-related increases in oxidative stress, inflammation and endothelial dysfunction are driven by, or associated with, increased systemic lipopolysaccharide leading to reduced cerebrovascular function and cognition, beyond normal ageing, have not been elucidated. Hence, this review examines how increased concentrations of lipopolysaccharide and the subsequent increased TLR4 activation observed in obesity exacerbate the development of obesity-induced reductions in cerebrovascular function and cognition.

1. Introduction

The gut-brain axis is composed of the complex interactions between the gastrointestinal tract (GIT), the GIT microbiota and the nervous system, which is mediated through complex endocrine, immune and metabolic interactions of all components of this axis [1–3]. The afferent and efferent neural connections act primarily as the relaying components of the nervous system that crosstalk with the GIT and GIT microbiota locally to further influence function of the central nervous system [2]. Therefore, the GIT microbiota can both indirectly and directly influence this axis and the functions of the central nervous system, including cognitive function [1,4]. Specifically, dysregulation of the immune system due to GIT dysbiosis can disrupt neural connections, leading to cognitive decline [1].

The GIT microbiota and its association with the lifetime risk of vascular disease, via immune activation and inflammation, has been an emerging field of research [5–7]. Although multiple associations between dietary and lifestyle factors and their impact on the GIT microbiota leading to disease have been studied, the effect of the GIT microbiota on cerebrovascular function is still an area of needed research [1,4]. In particular, the role of lipopolysaccharide (LPS)-induced inflammation that influences endothelial dysfunction which underlies cerebrovascular dysfunction and cognitive impairment is poorly described [7]. Therefore, the aim of this review is to: 1) briefly outline the obesity-induced changes to the GIT microbiota; 2) describe how LPS influences systemic inflammation leading to endothelial dysfunction; and 3) describe how these changes may induce cerebrovascular dysfunction and cognitive decline.

2. The GIT microbiota

Since the discovery of microbes within the GIT in the early 1890s, bacterial consumption was first postulated to be associated with improved digestive health and longevity [8–10]. Eli Metchnikoff was the first to propose that seeding the GIT with healthy bacteria could prevent the colonisation of harmful bacteria and, in turn, modify the GIT

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microbiota, conferring potential health benefits [8,10]. Since these foundational discoveries, research and information on the GIT microbiota have increased exponentially, particularly in the past 25 years [8,9].

2.1. GIT microbiota composition

Recent estimates approximate that there are in excess of 3.8–3.9 × 10^{13} bacterial cells that comprise the human microbiome, with the majority of these residing in the GIT [11]. The size of this microbial population far exceeds all other microbial communities associated with the body's surfaces [12,13]. Varying amounts of microorganisms live in a commensally symbiotic relationship in the human GIT and are collectively known as the GIT microbiota [1,8,12,14].

Although many microbes occupy the human GIT, the major phyla are Firmicutes, Bacteroidetes, Actinobacteria, Verrucomicrobia, Proteobacteria and Euryarchaeota [9,15,16]. Firmicutes and Bacteroidetes are the dominant phyla, comprising approximately 90 % of the GIT microbiota [12,17]. There are more than 200 separate species that form the phylum Firmicutes, including Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminococcus [17,18]. Firmicutes are generally gram-positive bacteria but do include some gram-negative species, such as the Negativicutes [19]. Bacteroidetes are gram-negative bacteria, with the most abundant genus being Bacteroides and Prevotella [17,20].

A study of faecal samples from 13 obese, and 13 non-obese volunteers revealed *Firmicutes* to be significantly enriched, while *Bacteroidetes* were significantly lowered in obese individuals [21]. This finding is supported by a systematic review of 32 research articles that assessed the GIT microbiota profiles of adult humans [22]. The review found that the adult human obese phenotype had a greater ratio of *Firmicutes/Bacteroidetes* compared to lean adult phenotypes. In obesity and associated disorders, including metabolic syndrome, gram-negative phyla such as *Verrucomicrobia*, have been shown to not change significantly. Whilst specific strains within the phyla, such as *Akkermansia muciniphila,* may decrease [23]. Therefore, in the obese adult phenotype, a shift in *Firmicute/Bacteriodete* ratio is seen (Fig. 1) [24]. Further, *Actinobacteria* increases with obesity, whilst *Verrucomicrobia* (mainly *Akkermansia municiphila*) decreases [25]. *Euryarchaeota* and *Proteobacteria,* however, remain relatively similar [24,25]. These microbial shifts influence GIT dysbiosis which leads to gut-brain axis dysregulation via increased systemic LPS, reactive oxygen species and inflammation [26–29].

2.2. GIT microbiota function

It is well established that an increased diversity and population of microbes inhabiting the GIT contribute to improved immunologic and metabolic functions [19]. The GIT microbiota assists in the biosynthesis of enzymes, vitamins, amino acids, and chemical transmitters, such as serotonin, which influences gut-brain communication, and the production of short-chain fatty acids (SCFAs) [17,30,31]. *Firmicutes* and *Bacteroides* assist with the digestion of pectin, amylose and amylopectin which are starches resistant to human digestive enzymes [20,32]. This digestion produces metabolites including the SCFAs *propionate, butyrate* and *acetate* [33–35]. *Propionate* provides energy to epithelial cells and is used in gluconeogenesis [30,36,37]. SCFAs also provide protection against pathogens [33,38]. For example, *Clostridium butyricum,* which produces *butyrate*, directly inhibits *Clostridium difficile* growth and metabolism, thus preventing diarrhoea and colitis in C57BL/6 WT mice [39]. Further, *Escherichia coli* (*E. coli*) metabolises glucose and secretes *acetate* and, in animal models, acetate can then enter the systemic circulation and modulate metabolic functions including thermogenesis [40,41]. *Acetate* also promotes T-cell differentiation to T cells that produce anti-inflammatory cytokines, such as interferon-γ and interleukin (IL)-10 [42,43]. This demonstrates how dietary changes can also influence the composition of the GIT microbiota.

The human GIT microbiota can also assist in the degradation of toxic compounds, such as oxalates by gram-negative *Proteobacteria*, and *Oxalobacter formigenes* [44]. Further, the *Firmicute*, *Eubacterium ramulus* cleaves the heterocyclic C-ring of flavonoids, phenolic compounds found in fruits and vegetables, and releases 3,4-dihydroxyphenylacetate, which has been shown to inhibit proliferation of colon cancer cells [37,45]. Therefore, the GIT microbiota can assist in the metabolism of food substances and can be anti-carcinogenic [20]. This makes the GIT microbiota a vital component in ensuring the optimal function of the GIT via pathogen protection, sequestration of nutrients and energy production [17,46]. The GIT microbiota also modulates plasma levels of LPS, an endotoxin released from the cell wall of gram-negative bacteria, which is a key activator of the innate immune system, specifically toll-like

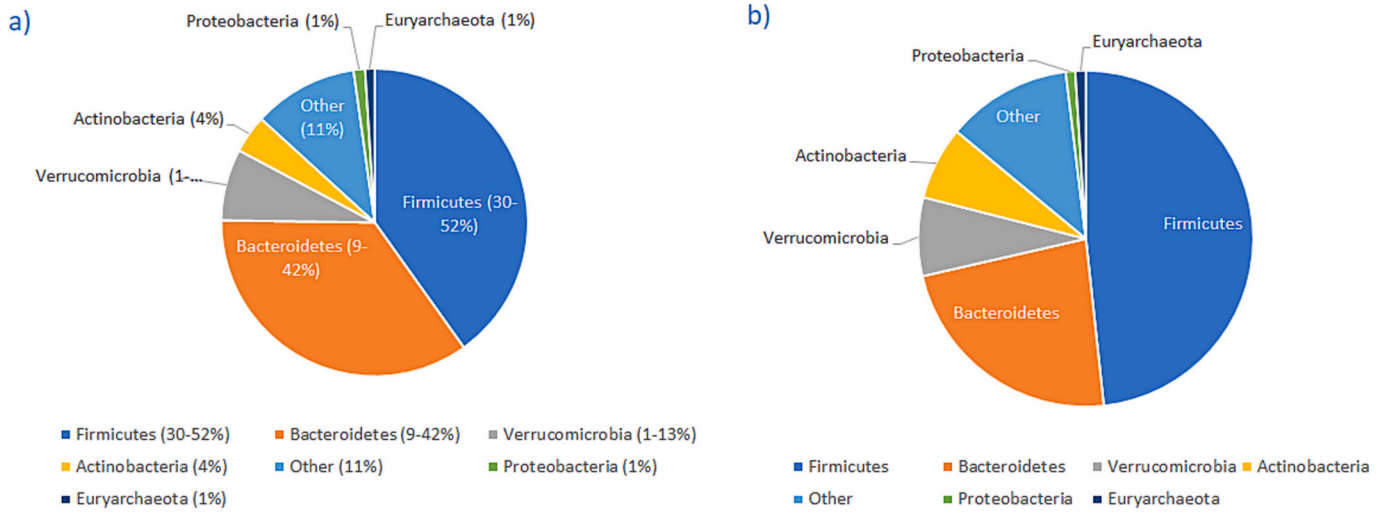

Fig. 1. Average gastrointestinal tract (GIT) microbiota phylum distribution of lean (a) and obese (b) humans [24,25,143,144]. In a typical lean adult, the GIT microbial composition of *Firmicutes* is generally 30–52 %, demonstrated as an average of 40 %. *Bacteroidetes* are generally between 9 %–42 %, represented as 35 %, and *Verrucomicrobia* the next largest, making up 1–13 %, represented as 8 % [24,25]. *Actinobacteria, Euryarchaeota* and *Proteobacteria* being less abundant and representing 4 %, 1 %, and 1 % respectively of the phyla in a lean adult [25,143,144]. The remainder of the phyla represents a combined total of 11 % [24,25]. In the obese adult phenotype, a shift in *Firmicute/Bacteriodete* ratio is seen, with *Firmicutes* averaging 48 %, and *Bacteroidetes* 23 % [24]. *Actinobacteria* increases with obesity, representing 7 % [143], whilst *Proteobacteria* decreases to 0.91 % [25]. *Euryarchaeota* stays relatively similar at 1 %. The remainder of the phyla represents a combined total of 12 % [24,25].

receptor (TLR) 4 [47].

2.3. GIT dysbiosis

Key factors that contribute to the development of an individual's microbiota composition include genetics, medications, age, stress, geographical location, and dietary and lifestyle habits [1,8,46,48]. These factors can cause a reduction of beneficial microbes, thus allowing opportunistic and pathogenic microbes to occupy the GIT [49]. This imbalance, which favours pathogenic microbes, causes disruptions in GIT function, leading to GIT dysbiosis and disease susceptibility [49,50]. Therefore, a reduced quantity or diversity of beneficial GIT microbiota has been associated with a predisposition to inflammation and disease development, including irritable bowel disease [51], and obesity [15].

3. Obesity, GIT microbiota and cognition

Obesity is a global health priority, currently affecting two billion people worldwide [52,53]. Increased adiposity is a key feature of obesity, which is a preventable and modifiable low-grade systemic inflammatory metabolic disease [54]. Obesity is typically associated with an energy-dense, high-fat, high-carbohydrate and highly palatable Westernised diet [4,15,55]. Chronic intake of this diet promotes GIT dysbiosis, GIT permeability and systemic circulation of LPS [54,56]. Further, de La Serre et al. [57] reported that after consuming either eight or 12 weeks of a high-fat diet, male Sprague-Dawley rats had increased activation of TLR4 within the GIT, alongside increased GIT permeability, increased plasma LPS and systemic inflammation. The authors suggested that this was due to a decrease in the total bacterial count and an increase in the relative proportion of *Bacteroidales* and *Clostridiales*. In support of this, LPS neutralisation using the antimicrobial peptide 19–2.5 in mice fed with a high-fat diet showed a decrease in the production of the inflammatory cytokine tumour necrosis factor-alpha (TNF-α) [58,59]. Therefore, obesity promotes GIT dysbiosis and chronic low-grade systemic inflammation resulting from increased activation of TLR4 by LPS, which, in turn, may promote endothelial dysfunction (Fig. 2). This figure shows that a high-fat, high-carbohydrate diet causes shifts in microbiota composition, resulting in dysbiosis, increased systemic circulation of LPS which activates the innate immune system via TLR4 activation, leading to chronic systemic low-grade inflammation. Microbial dysbiosis, increased LPS and inflammation all lead to vascular endothelial dysfunction, a main underlying factor of vascular impairment [7,54,56].

Obesity may have differential effects depending on the arterial site. A prospective study found severely obese children to have significantly lower carotid arterial compliance and distensibility, with both flow-mediated and glyceryl-trinitrate-mediated dilation being significantly lower compared to healthy controls [60]. Additionally, Kappus et al. [61] found that obese male subjects had significantly greater carotid artery stiffness compared to the normal weight subjects. This is due to chronic inflammation of the vascular wall, leading to larger arteries with low shear stress, causing maladaptive remodelling of arterial sites [62]. This indicates obesity-induced gut dysbiosis which causes increased LPS immune system activation and, therefore, systemic inflammation could be a main driver leading to endothelial dysfunction, which underlies increased arterial stiffness and reduced compliance. Obesity-induced endothelial dysfunction is a risk factor for cardiovascular disease and therefore a risk factor for cerebrovascular disease due to hypoperfusion, which changes the structure and function of the brain leading to cognitive decline.

Observational studies have also found that obesity increases the risk of dementia between 32 and 45 %, due to increased concentrations of inflammatory cytokines, such as IL-6 and high-sensitivity C-reactive protein [63]. Further, Bliss et al. [64] reported that patients with metabolic syndrome, who were physically inactive, had significantly reduced cardiovascular, cerebrovascular and cognitive functions. Obesity is associated with chronic low-grade systemic inflammation, impaired endothelial function and reduced cardiometabolic health [54,56]. Therefore, increased adiposity induces inflammation which can impair vascular function and reduce cardiovascular function. This causes cardiovascular disease and reduces cerebral blood flow (CBF), which leads to hypoperfusion and cognitive decline [65,66].

4. Cerebrovascular function

Cerebrovascular function describes the ability of the cerebrovasculature to perfuse the brain with adequate blood (i.e., CBF) in response to physical and psychological stimuli [67,68]. This is achieved through neurovascular coupling (NVC) and cerebral autoregulation [67]. The brain is one of the body's most metabolically active organs, consuming between 15 and 20 % of the body's nutrients and energy under resting conditions [69]. As the brain cannot store nutrients and oxygen, it requires a constant supply of these through the CBF to function optimally and maintain its primary functions, particularly cognition [70]. Changes in cerebral blood pressure, perfusion pressure, vascular diameter, and blood viscosity all affect CBF [71–73]. CBF is maintained by the cerebrovasculature, which supports brain function by responding to physical and psychological stimuli, thus ensuring adequate CBF [67,68]. Autoregulation ensures that a constant mean arterial pressure of 50–160 mmHg is maintained in response to chemical and/or mechanical stimuli [67,68]. This response is largely initiated by either increased (vasodilatation) or long-term decrease (vasoconstriction) of nitric oxide (NO) metabolism, which regulates the resistance applied globally to the cerebrovasculature [70,74]. Conversely, during NVC neurons communicate with endothelial cells to release vasodilatory mediators, such as NO, which maintains CBF locally during periods of increased neuronal metabolism [74,75]. Both cerebrovascular function and cognition are reduced by unmodifiable risk factors (ageing and genetics) and modifiable lifestyle factors which promote obesity development and reduced cardiovascular function [76]. Morys et al. [77] undertook an observational eight-year follow-up cohort study, which included over 20,000 general community participants with a mean age of 63 years and reported that obesity was associated with increased inflammatory markers, particularly high-sensitivity C-reactive protein and increased cerebrovascular disease. This in turn was associated with lowered cortical thickness and volume and cognitive deficits. The central mechanism leading to cerebrovascular dysfunction and decreased cognition is a chronic increase in oxidative stress, inflammation and impaired endothelial function [70,78–82].

5. Lipopolysaccharides and Toll-like receptor 4

LPS is an endotoxin found abundantly in the outer membrane of gram-negative bacteria [83,84]. LPS contains a hydrophobic portion, known as lipid A, which is attached to a central oligosaccharide and a distal polysaccharide, or O antigen (Fig. 3) [85,86]. The presence of LPS provides bacterial resistance to substances such as antibiotics [86]. LPS is released from bacteria during cell division and cell death [87].

LPS are the most studied of the pathogen-associated molecular patterns (PAMPs) [83]. PAMPs are antigens recognised by pattern recognition receptors, such as toll-like receptors (TLRs) [88,89]. TLRs are proteins expressed on the cell surface of cells that comprise the innate immune system, which functions to recognise conserved microbial structures including LPS [85,86]. Specifically, LPS is recognised predominantly by TLR4, which is a lipid A signalling receptor [85,90]. TLR4 is found in the plasma membrane of myeloid-derived leucocytes, such as macrophages, as well as other cell types including adipocytes, vagal afferents, and epithelial cells [1,85,91,92].

TLR4 has an extracellular leucine-rich repeat, a single transmembrane segment and a smaller cytoplasmic signalling region that engages the adaptor protein, myeloid differentiation primary response 88 (MyD88) [85,93]. The stimulation of TLR4 by LPS promotes MyD88

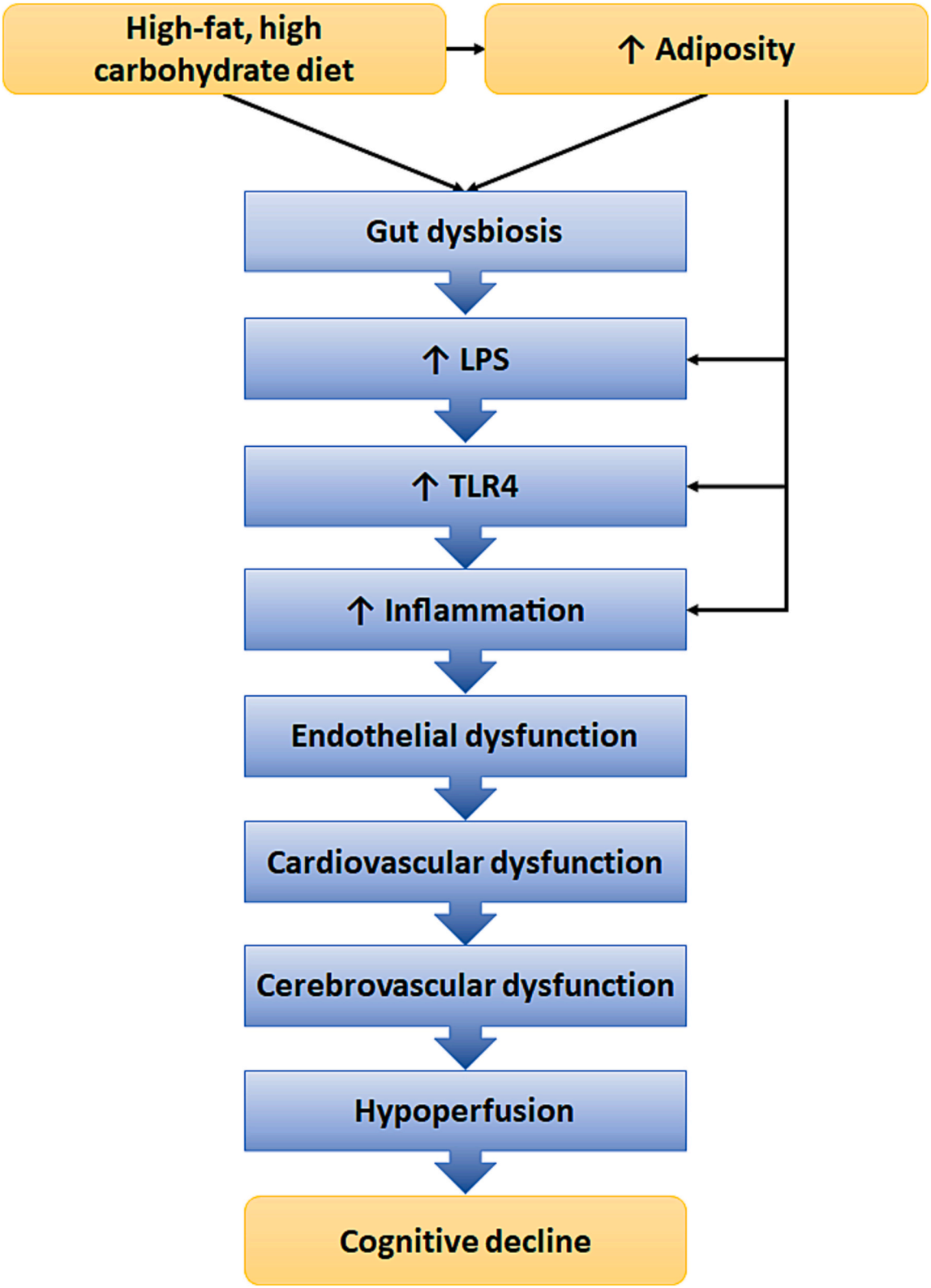

Fig. 2. Overview of how a high-fat, high-carbohydrate diet can lead to cognitive decline. A high-fat, high-carbohydrate diet, often associated with increased adiposity, causes shifts in GIT microbiota composition, resulting in dysbiosis which creates an increase in lipopolysaccharides (LPS), produced by increased turnover of gram-negative bacteria [54,56]. This shift also increases GIT permeability which allows the transport of opportunistic bacteria through an otherwise impenetrable GIT barrier, resulting in inflammation and increased passage of LPS [100,101]. Further, high-fat diets increase the presence of chylomicron formation which assist transportation of LPS into the systemic circulation [54,56]. Obesity also increases toll-like receptor TLR4 expression within the gut [57]. LPS activates the innate immune system via TLR4 activation which causes increased cytokine production leading to chronic systemic low-grade inflammation [85,91,95]. Microbial dysbiosis, increased LPS and inflammation all lead to vascular endothelial dysfunction [7,54,56]. Endothelial dysfunction is a risk factor for cardiovascular disease and therefore a risk factor for cerebrovascular disease, due to hypoperfusion which changes the structure and function of the brain, leading to cognitive decline.

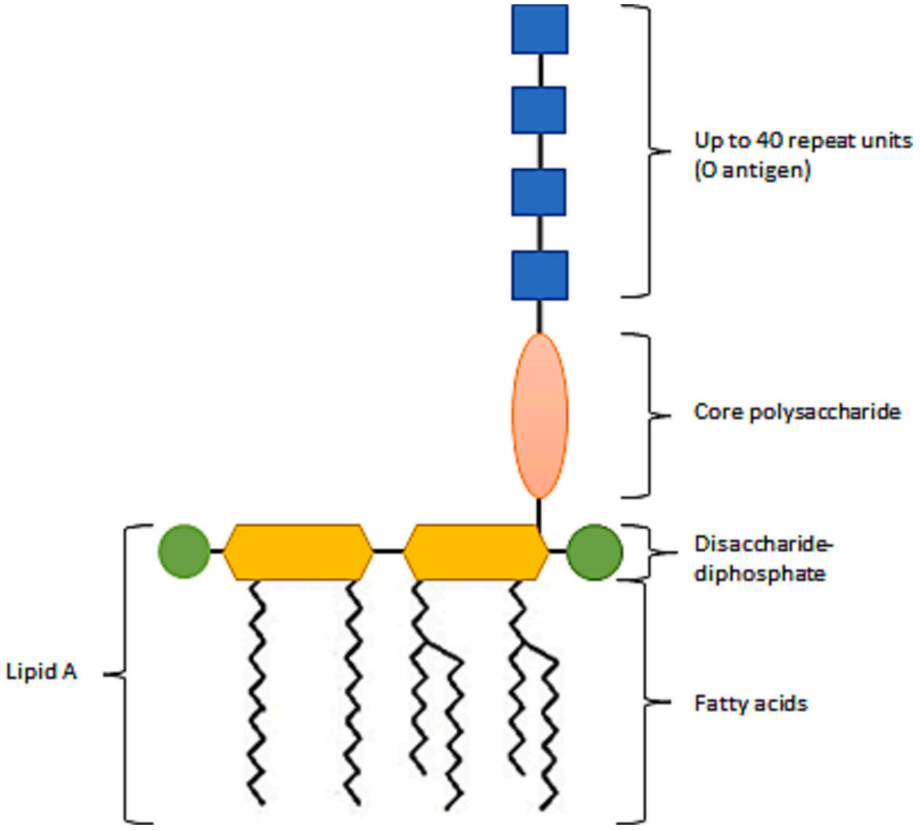

Fig. 3. Lipopolysaccharide (LPS) structure. LPS contain a hydrophobic portion, known as lipid A made of a fatty acid and disaccharide-diphosphate. The lipid A section of LPS is responsible for the activation of TLR4. LPS also contain a non-repeating core oligosaccharide and distal O-antigen polysaccharide make up the hydrophilic portion of LPS [85,86].

intracellularly to TLR4 via a homophilic interaction [91]. MyD88 then promotes interleukin-1 receptor-associated kinase 4 (IRAK4) to the site which phosphorylates IRAK downstream, in turn recruiting tumour necrosis factor receptor-associated factor 6 (TRAF6) [94]. The IRAK-TRAF6 complex then disassociates from the TLR4 receptor and activates TGF-β-activated kinase 1 (TAK1), leading to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and c-Jun NH2-terminal kinase (JNK) [94]. This results in the downstream signalling cascade and production of proinflammatory cytokines and chemokines such as TNF-α, IL-1, IL-6 and IL-8 [85,91,95]. A high-fat, high-carbohydrate diet, which is associated with obesity, increases the presence of both LPS and TLR4 within the GIT, and increases the

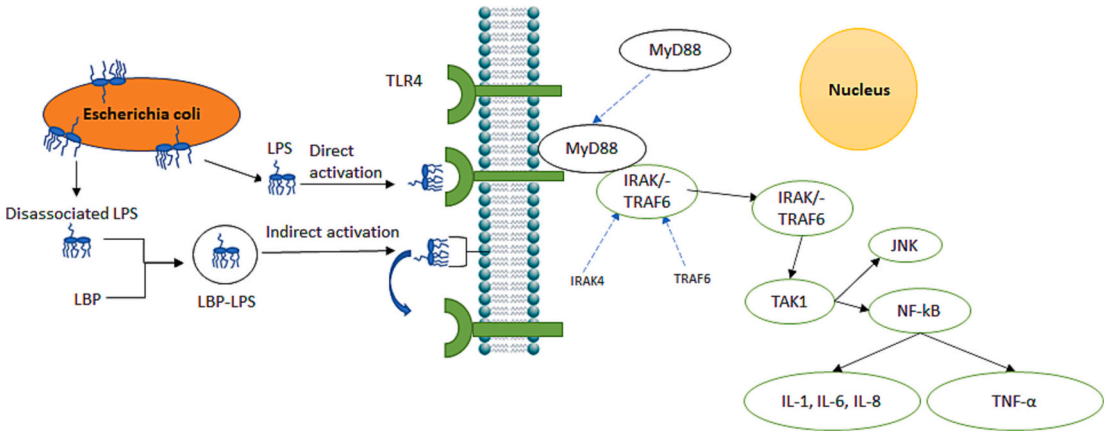

Fig. 4. Activation of toll-like receptor 4 (TLR4) by lipopolysaccharides (LPS). In the bloodstream, LPS activates TLR4, which promotes toll/interleukin receptor-1 protein, myeloid differentiation factor 88 (MyD88) to the cytoplasmic region of the TLR4 [91]. MyD88 promotes complex interactions that promote transcription factors, such as c-Jun N-terminal kinases (JNK) and nuclear factor kappa-light-chain-enhancer of activated b cells (NF-kB), in turn increasing the production of inflammatory cytokines, in particular interleukin (IL)-1, IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α) [90,94,95]. TLR4 can also be activated indirectly when LPS binds to LPS-binding protein (LBP) [91]. Here, LPS-LBP activates CD14 which promotes TLR4-MyD88 activation [145]. This further promotes inflammation and promotes vascular inflammation as the tight junction of the endothelium become compromised, leading to inflammatory cell infiltration of nearby tissue, or increased permeability of inflammatory cytokines into adjacent tissue [146]. Further, cytokines penetrate the blood-brain barrier, impairing its integrity and leading to reduced cerebral blood flow and therefore hypoperfusion causing changes in brain function and structure that precede cognitive decline [78].

systemic circulation of LPS [54,56]. This leads to an increase in proinflammatory cytokine production in obesity which contributes to chronic low-grade systemic inflammation [96].

5.1. LPS-induced activation of TLR in obesity

Chronic stimulation of the immune system is not beneficial and can promote chronic low-grade inflammation [80]. This can result when GIT microbes interact with pattern recognition receptors expressed by epithelial cells, leucocytes and the central nervous system [97], through the activation of TLR4 by LPS [50,80,84,98]. Increased and sustained biosynthesis and export of LPS by gram-negative bacteria, such as *E. coli* and *Klebsiella pneumonia,* within the GIT will promote increased TLR4 expression [99,100]. The increased concentrations of LPS will consistently activate TLR4, which promotes pathways such as NF-kB and mitogen-activated protein kinase (MAPKs), leading to a sustained increase of the inflammatory cytokines described above, including IL-6 and IL-8 (Fig. 4) [89,95]. This is particularly evident in a study of obese-prone rats where epithelial and immune cells were reported to have increased TLR4 expression and increased white adipose tissue inflammation when compared to obese-resistant rats. This coincided with an increased LPS concentration resulting from non-beneficial strains of gram-negative bacteria and an abundance of *Firmicutes* within the GIT [99].

Obesity also increases the intestinal absorption of LPS, therefore increasing systemic circulation of LPS [84]. This increase in LPS promotes dysfunction of the tight gap junctions between epithelial cells which increases GIT permeability [100]. GIT permeability allows the passage of otherwise impenetrable substances to pass through the epithelium [101]. The release of LPS systemically, due to increased GIT permeability, induces inflammation by increasing NF-kB expression via increased TLR4 activation [95].

High-fat diets leading to obesity, also increase plasma concentrations of LPS through increased chylomicron transport [47,102]. Chylomicrons are water-soluble transporting vehicles whose main function is to transport lipids into systemic circulation [103]. Chylomicrons transport LPS via exocytosis from absorptive cells of the intestinal lumen into the systemic circulation [104]. Therefore, high-fat diets that lead to obesity, increase chylomicron formation and transportation of fats to adipose tissue, as well as LPS into systemic circulation [103]. Further, the increase in plasma LPS contributes to insulin sensitivity, which in turn increases adiposity, and therefore obesity [47,101]. This cycle persists whereby increased adiposity further increases LPS through dysbiosis and the increased LPS further increases adiposity [47]. *E. coli* was supplemented alongside an energy-dense diet in rats, from foetal life through to six months [105]. It was found that the *E. coli* group had increased weight gain and plasma leptin levels, as well as lowered microbe diversity compared to the control group who were only fed an energy-dense diet. Additionally, the GIT microbe diversity was lowered in the *E. coli* group compared to the control group. This was in contrast to the group supplemented with *Lactobacillus plantarum* (*L. plantarum*) which demonstrated increased microbe diversity and lower levels of weight gain compared to both the control and *E. coli* groups, as well as lower retroperitoneal adiposity and plasma leptin levels than the *E. coli* group. This study demonstrated the effects of increased *E. coli*, from conception onward, on increasing adiposity, and the effects of *L. plantarum* in reducing adiposity and associated biomarkers, such as leptin, supporting the cycle of GIT microbial changes influencing obesity and vice versa.

5.2. LPS and endothelial dysfunction

Vascular endothelial cells line the entire cardiovascular system and play an important role in regulating vascular tone [106]. The healthy endothelium has a vasodilatory phenotype with low levels of reactive oxygen species and high levels of vasodilators, such as NO which promotes sustained vasodilation and, therefore, increased blood flow [74,106]. Endothelial nitric oxide synthase (eNOS) primarily synthesises NO. However, the uncoupling of eNOS due to increased age or systemic inflammation reduces NO production and increases superoxide production concurrently, thus promoting increased oxidative stress [106]. The overexpression of inflammatory cytokines resulting from increased activation of TLR4 by LPS stimulates the attachment of leukocytes to the endothelium [107]. This results in increased vascular permeability, oxidative stress, and occlusion of vessels which promotes the uncoupling of eNOS and a continued cycle of increased oxidative stress and low-grade systemic inflammation [70,108,109]. Further, LPS-induced activation of TLR4 promotes oxidative stress through increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [110,111]. When NADPH is reduced by NADPH oxidase, superoxide is generated, which subsequently uncouples eNOS and reduces NO bioavailability thereby promoting endothelial dysfunction [112] Increased NADPH oxidase activity also reduces the bioavailability of NADPH which is an essential co-factor for NO production, thus further promoting oxidative stress and endothelial dysfunction [113]. Free-fatty acids contribute to the chronic low grade systematic inflammation seen in obesity via TLR4 activation. [114]. This activation also contributes to chronic inflammatory conditions and obesity-related comorbidities, such as insulin resistance and vascular dysfunction [115]. The increase in inflammation and vascular dysfunction resulting from increased free-fatty acid concentration in obesity is complex and involves multiple pathways which have been reviewed in detail previously [115]. However, one of the most prevalent mechanisms by which increased free-fatty acids contribute to endothelial dysfunction is by increasing NAPDH oxidase activity thus increasing reactive oxygen species generation, namely superoxide, which uncouples eNOS and reduces NO bioavailability [115,116]. Further, LPS can act independent of TLR4 to induce inflammation in obesity [117]. Inflammatory caspases assemble in the cytosol of epithelial cells and macrophages and can sense LPS intracellularly and activate inflammasomes [118]. Activation of inflammasomes leads to cell lysis and extracellular release of proinflammatory cytokines, such as IL-1β and IL-18, exacerbating the inflammatory response [119].

This causes reduced vascular compliance and increased atherosclerotic formation, thus reducing systemic blood flow [78]. As this cycle progresses, local ischaemia and microvascular haemorrhages may result, which reduces capillary density, impairs blood-brain-barrier integrity and function, thus reducing CBF [55,64]. Simply, reduced endothelial function impairs the ability of the cerebrovasculature to maintain CBF (i.e., impaired cerebrovascular function), thus resulting in cerebral hypoperfusion and unfavourable cerebral structural and functional changes leading to cognitive decline [78].

Additionally, this cycle of events can promote leukoaraiosis, microglial activity and astrocyte secretions [120,121]. For example, Qin et al. found that a single LPS intraperitoneal injection of 0.5 mg/kg activated microglia in mice. Microglia are immune cells found in the brain that act to clear neuronal damage [120]. Increased microglia activation is a key in the pathogenesis of many neurodegenerative diseases, such as Alzheimer's disease [120]. Therefore, LPS-induced systemic inflammation promotes neuroinflammation and accumulation of neurotoxic molecules, such as amyloid-β, as well as the reduction of molecules, such as brain-derived neurotrophic factor (BDNF), that are responsible for maintaining neuronal development and volume [122,123]. This further impairs cerebrovascular function and cognition via impaired neuronal communication and function and increases neuronal destruction culminating in neurodegeneration and, eventually neurodegenerative diseases, such as dementia. Hence, endothelial-derived NO is, therefore, one of the most important signalling molecules for maintaining CBF, and a potential target for preventing cerebrovascular and neurodegenerative diseases [122,123].

6. How systemic inflammation impairs gut-brain communication

Reflex arcs are basic central nervous system responses to environmental changes [124]. The nervous system reflex arc is composed of sensory (afferent) neurons, that receive information from receptors and send this to the central nervous system which mounts a response to the stimuli via motor (efferent) neurons [125]. Reflex arcs are a sympathetic nervous system response to potentially threatening situations [124]. For example, pro-inflammatory cytokines activate afferent sensory neurons that signal the brain which mounts an efferent response to the spleen (target tissue), to regulate NF-kB, therefore reducing inflammation (Fig. 5) [126,127].

The vagus nerve traverses the central nervous system to the GIT, with thoracic and cervical afferent fibres that innervate the oesophagus, heart, aorta and GIT [128]. The vagal afferent system can therefore detect immune-related events in the periphery and generate autonomic, endocrine, and behavioural responses via central nervous system reflex pathways [128]. We have previously described these pathways [15]. Briefly, TLR4 is present in vagal nerve endings throughout the GIT [129]. Locally, LPS activates TLR4 on the vagal nerve within the GIT lamina propria and muscularis externa layers of the GIT [128,130]. Systemically, LPS activates the TLR4 receptors on the inferior ganglion (nodose ganglion) of the vagus nerve [131]. Further, increased activation of the immune system due to LPS-induced GIT dysbiosis, and subsequent vagus nerve activation, can enlarge the spleen (splenomegaly). The spleen plays a key role in immune regulation and mediates the pro-inflammatory effects of the vagus nerve in sleep-deprived mice [132,133]. The inflammatory pathways induced by LPS have been shown to cause splenomegaly, as well as a depression-like phenotype, due to increase systemic inflammation and neuroinflammation [133]. On the other hand, stimulation of afferent vagus nerve fibres by non-pathogenic bacteria within the gut influences neurotransmitters, such as serotonin and dopamine, therefore playing a crucial role in the reduction of major psychiatric conditions, such as mood and anxiety disorders [132]. This activation increases sympathetic nervous system activities, whilst subdiaphragmatic vagotomy post LPS injection in mice was shown to attenuate splenomegaly and reduce systemic inflammation [132]. Additionally, subdiaphragmatic vagotomy post LPS injection in mice was reported to improve GIT microbiota composition, reduce systemic inflammation and blocked depression-like behaviours [134], while subdiaphragmatic vagotomy post LPS and IL-1 injection improved food-motivated behaviours compared with mice that were not vagotomised [135]. Therefore, unfavourable changes in the GIT microbiota that result in increased systemic or localised LPS, which both occur in obesity, cause systemic inflammation and activation of the vagus nerve innervating the lamina propria and muscularis layers of the GIT. This can then further lead to central nervous system regulation which can have a profound impact on the immune response, and behavioural type disorders via vagus nerve stimulation [136].

Bercik et al. [137] induced GIT inflammation by infecting albino mice with the non-invasive parasite *Trichuris muris,* which caused anxiety-like behaviour associated with decreased hippocampal BDNF [137]. The reduction of BDNF results in reduced neuronal growth and neuroplasticity and has therefore been associated with dementia development [122,138]. This, therefore, promotes inflammatory processes in the brain and systemically could contribute to cerebrovascular dysfunction via vagal nerve stimulation, thus exacerbating cognitive

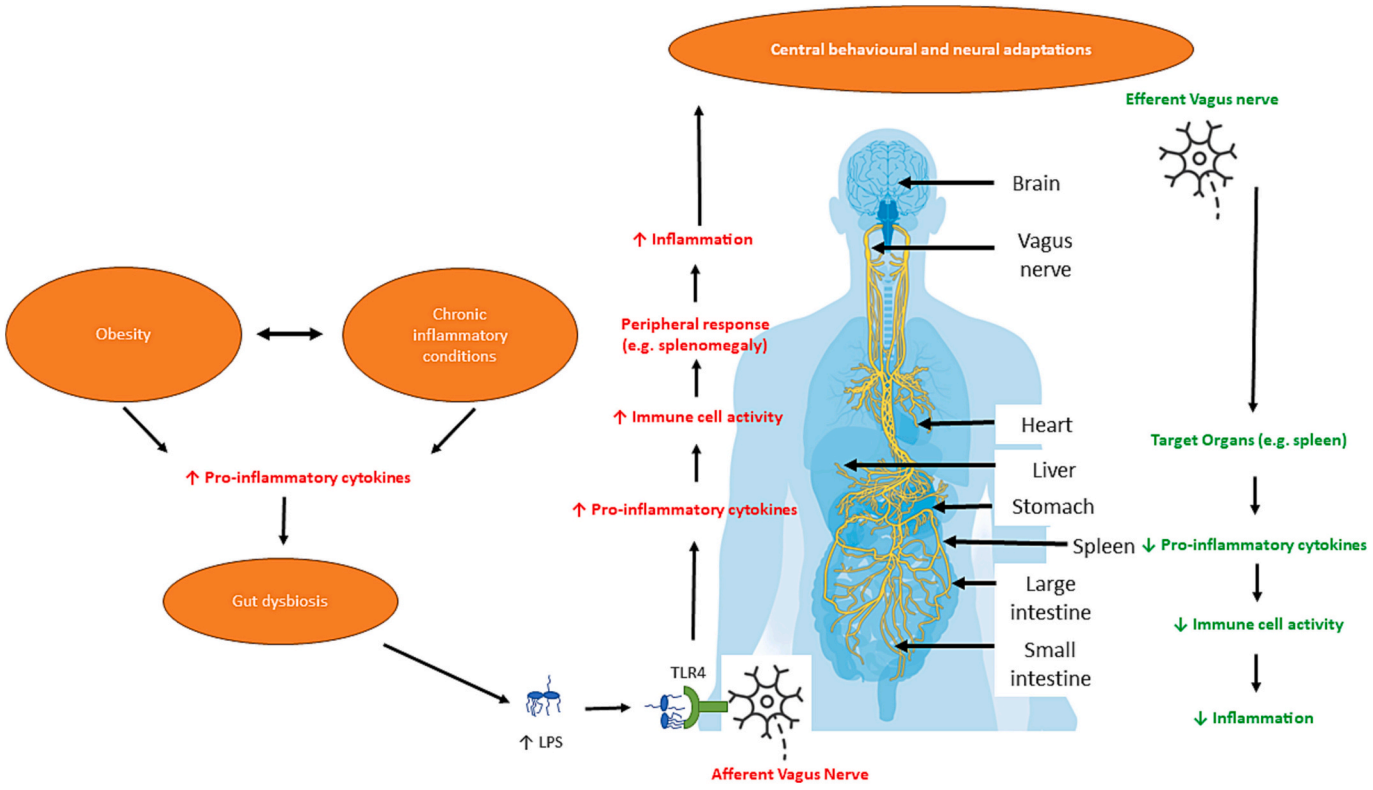

Fig. 5. Demonstration of the inflammatory reflex arc. The vagus nerve is the longest nerve in the body and innervates the brain, heart, liver, stomach, spleen and intestines [128]. Gut dysbiosis, which can result from obesity and/or other chronic inflammatory conditions, typically occurs and results in an increase in gram-negative bacteria abundant in lipopolysaccharides (LPS) [26–29]. Locally LPS binds and activates toll-like receptor 4 (TLR4) on afferent vagus nerve fibres within the gut [130,147]. This activation creates a cascade that inreases pro-inflammatory cytokines and the immune system, namely macrophage activation [91]. This can result in a mounted peripheral respone and induce splenomegaly, which can occur due to the increased inflammation and, therefore, workload on the spleen to perform immune modulating actions [132,133]. The spleen is one of the target tissues of the efferent vagus nerve fibres communication and, as such, acts to downregulate inflammation [126,127].

decline. Therefore, this demonstrates how changes in the GIT microbiota have been linked to memory and learning which indicate a cognitive influence from the GIT microbiota [139].

7. Future directions

The information outlined in this review provide insights into obesity-driven increases in LPS which cause gut dysbiosis and inflammation which activate the immune response and precedes endothelial dysfunction, a key underlying mechanism that leads to cardiovascular disease and cognitive decline. Therefore, inhibition of inflammatory mechanisms and the management of obesity can assist in reducing the risks associated with cardiovascular and cerebrovascular complications.

Pharmacological treatments, such as atrovastatin, katamine and melatonin and natural supplementation, such as resveratrol, have been explored in animal models to assist in alleviation LPS-induced neuroinflammation, behavioural and cognitive dysfunction. Treatments that target LPS-derived TLR4 activation, gut dysbiosis or vagus nerve stimulation and its subsequent inflammatory pathways could be a potential intervention to prevent cognitive decline. Research examining the interactions by which obesity-related increases in LPS exert inflammatory effects that lead to cognitive decline may provide novel information on the pathogenesis of obesity-associated gut dysbiosis, increased LPS and further clues for the development of new therapeutic strategies.

8. Conclusions

The increasing epidemic of obesity is a global health priority [53]. With the concomitant increase in worldwide neurodegenerative diseases, such as dementia, it is important to examine underlying mechanisms that may contribute to cognitive decline in obesity. Preliminary evidence suggests that the GIT microbiota may play a role in cerebrovascular dysfunction and cognitive decline in obesity. The gut-brain axis is a well-studied, yet emerging field of research. However, the mechanisms by which increased LPS resulting from gut dysbiosis observed in obesity result in vascular impairment and, therefore cerebrovascular dysfunction and cognitive decline have not been fully elucidated.

Trillions of microorganisms inhabit the GIT, with the major phyla being *Firmicutes* and *Bacteroidetes*. The structure of the human GIT, along with the typical lean adult GIT microbiota phenotype ratio of *Firmicute/Bacteroidetes* provides a unique environment that resists the ability for opportunistic pathogens to enter systemic circulation, therefore preventing inflammation and disease [28,140]. However, obesity drives GIT microbial imbalances, which shifts the *Firmicute/Bacteroidetes* ratio, allowing opportunistic bacterial growth, thus leading to increased gram-negative bacteria containing an abundance of LPS [29]. Additionally, the intake of a high-fat, high-carbohydrate Westernised diet, which is associated with obesity, increases the production of chylomicrons, which promote the transport of LPS into systemic circulation [103,104]. These GIT microbial shifts also increase GIT permeability and therefore the passage of opportunistic pathogens to enter systemic circulation which increases systemic inflammation [47]. These actions increase both GIT and systemic LPS concentrations.

LPS increases cytokine production via the activation of the innate immune system, and more specifically activation of TLR4 found on GIT vagal nerve afferents and immune cells, such as macrophages [91]. GIT TLR4 expression is also increased in the obese phenotype, leading further to increased activation of TLR4 by LPS [54,56]. The activation of TLR4 promotes inflammatory cytokine production through intracellular mechanisms that activate MyD88 and produce inflammatory markers, such as NF-kB, IL-1, IL-6, and IL-8 [85,91,95]. These inflammatory markers increase systemic inflammation, causing the uncoupling of eNOS which reduces NO production and concurrently creates increased superoxide production [70,106,141]. This promotes oxidative stress, further contributing to inflammation and endothelial dysfunction which causes reduced vascular compliance, thus reducing systemic blood flow. Local ischaemia and microvascular haemorrhages may result, which cause impairment to the blood-brain-barrier integrity, thus reducing CBF. Therefore, reduced endothelial function as a result of activation of TLR4 by LPS, impairs the ability of the cerebrovasculature to maintain CBF, resulting in hypoperfusion and structural and functional changes in the brain that precede cognitive decline.

Despite how LPS may contribute to the advance in cognitive decline seen in obesity, the effect of the GIT microbiota on cognition is an important area of research [1]. The underlying mechanism correlating increased obesity, GIT microbiota, LPS, inflammation and cerebrovascular dysfunction to cognitive decline requires further investigation. Specifically, whether cognitive changes are driven by cerebrovascular events influenced by the GIT microbiota, remains to be fully elucidated [31,142]. Future studies should aim to investigate specific GIT microbiota changes in obesity, compared to lean phenotypes, and how this may relate to cerebrovascular function and cognition. Analyses of GIT microbiota concentrations and changes alongside cerebrovascular, cognition and neuronal connectivity (the gut-brain-microbiota axis) during obesity may assist in the development of new treatment strategies to combat the growing epidemic of neurodegenerative diseases, such as dementia.

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CRediT authorship contribution statement

Tammy Thornton: Conceptualization, Writing – original draft, Writing – review & editing. **Dean Mills:** Writing – review & editing. **Edward Bliss:** Writing – review & editing.

Declaration of competing interest

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