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Reducing dietary lipopolysaccharides to slow progression of cognitive impairment and Alzheimer's disease

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ABSTRACT

We hypothesize that a dietary reduction of lipopolysaccharide (LPS) could reduce risk and slow progression of cognitive impairment and Alzheimer's disease by reducing neuroinflammation. LPS is a component of the highly inflammatory cell membrane of Gram-negative bacteria. LPS and inflammatory cytokines are elevated in Alzheimer's disease, both in plasma and in the central nervous system. Inflammatory cytokines, triggered by LPS in food, can enter the brain via active transport and induce microglial activation and inflammatory damage, including loss of synapses and neurons. Excess LPS and inflammatory cytokines can also induce blood-brain barrier damage and increase amyloid-β production. The highest dietary sources of LPS are processed meat and dairy products, which can rapidly raise levels of plasma LPS within one to two hours. For example, there was a 65-fold increase in plasma LPS after eating a thin-crust cheese pizza. The LPS in these foods is transported via chylomicrons into the bloodstream. Smaller amounts of LPS from colonic microbiota do not account for the sharp postprandial increase of plasma LPS. Once in the bloodstream, LPS can increase inflammatory cytokines 2-fold to 68-fold within two hours. LPS increases cytokines via LPS binding protein and cluster of differentiation-14, triggering toll-like receptor-4, and activating nuclear factor kappa-B. Nuclear factor kappa-B can increase cytokine levels, including interleukin-1-beta, interleukin-6, and tumor necrosis factor-alpha. Practical implications: Even low plasma levels of LPS can reduce cognition. Decreasing brain inflammation by reducing dietary LPS can lower risk of cognitive impairment and dementia.

Contribution: It has been previously thought that plasma lipopolysaccharides come only from infection or colonic bacteria. However, certain foods can be high sources of plasma lipopolysaccharides, which can raise plasma inflammatory cytokines. We have shown that eating more of these foods can increase risk of cognitive impairment and Alzheimer's disease.

1. INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent disorders among older adults, with over 55 million people worldwide suffering from dementia (Dementia, 2024). Identifying dietary lipopolysaccharide (LPS) as a contributing cause of AD and cognitive impairment can provide us with another way to reduce neuroinflammation: by adjusting the diet. It has been hypothesized that LPS from intestinal microbiota is the main contributor to plasma LPS (Rohr, Narasimhulu, Rudeski-Rohr, & Parthasarathy, 2020). There is insufficient LPS produced in the small intestine to account for the after-meal surge of plasma LPS (Laugerette, Vors, Peretti, & Michalski, 2011). Although LPS from colonic bacteria may contribute to plasma LPS, this chronic leakage cannot explain the spike of plasma LPS after a meal (Saji et al., 2022). LPS from certain foods can sharply increase plasma LPS from one to four hours after a meal.

We will examine how much LPS is in certain foods and how it enters the bloodstream (Vors et al., 2017). We examine the mechanisms of action whereby plasma LPS increases inflammatory cytokines (Figure 1). We explore how these inflammatory cytokines enter the brain, activate microglia, and damage delicate neurons (GBrown, 2019). Studies where humans are injected with tiny amounts of LPS show cognitive impairment within hours (André, Laugerette, & Féart, 2019). Diets containing high-LPS foods, such as meat, also increase cognitive impairment (Grant & Blake, 2023). Reducing dietary LPS may slow the progression of AD and cognitive impairment.
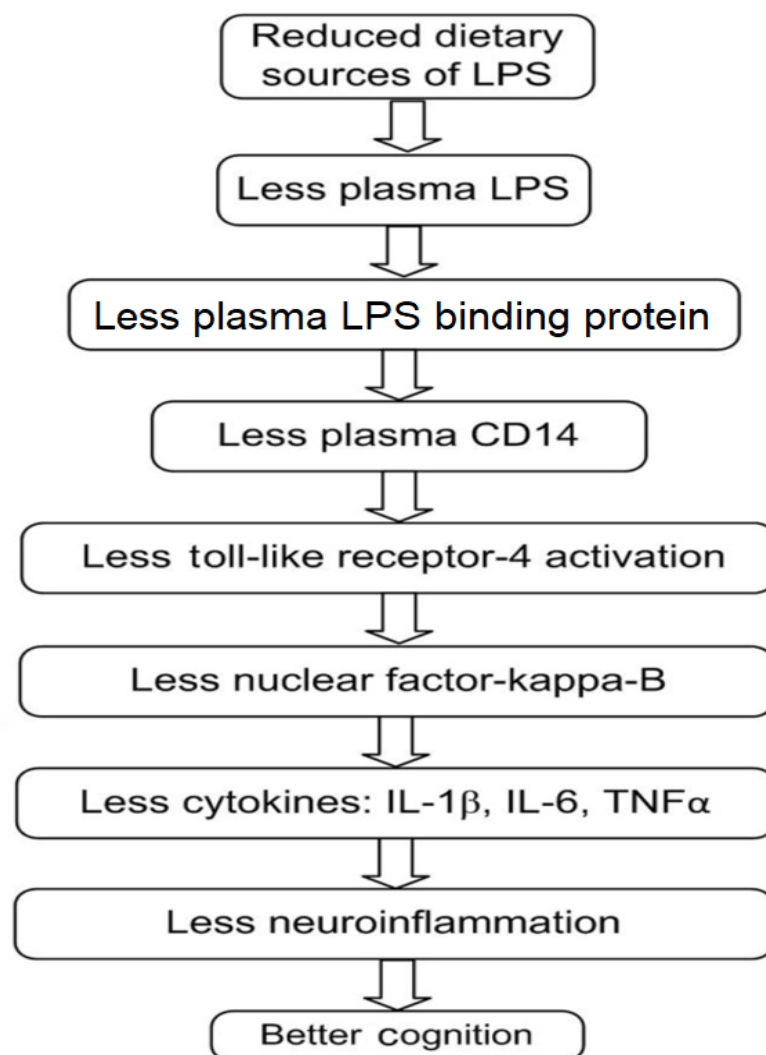

Figure 1. The proposed mechanisms leading to an improvement of cognition by reducing dietary LPS.
Note: LPS=Lipopolysaccharides, LBP=LPS binding protein, CD14=Cluster of differentiation-14, IL-1β=Interleukin-1-beta, IL-6= Interleukin-6, TNFα=Tumor necrosis factor-alpha.

2. WHAT ARE LIPOPOLYSACCHARIDES?

There are three potential sources of lipopolysaccharides (LPS): from bacterial infection, from colonic microbiota, and from food. LPS represents about 80% of the cell wall of Gram-negative bacteria. The terms LPS and endotoxin are used synonymously. LPS is a compound localized on the outer membrane of bacterial cells. LPS is made up of an antigen-O specific chain, a core region of a hetero-12 oligosaccharide, and a lipid A region that is the inflammatory part of the LPS (Laugerette et al., 2011). Toll-like receptor-4 (TLR-4) is a transmembrane receptor that can sense LPS and is expressed on the surface of monocytes and macrophages, dendritic cells, intestinal epithelial cells, and blood vessel endothelial cells (Andreasen et al., 2008). LPS can increase microglial reactive oxygen species (ROS) production, neurotoxicity, and phagocytosis of neurons (Brown, 2019). LPS from different Gram-negative bacteria can induce specific immune responses, which makes comparative studies difficult. LPS concentration is usually expressed in ng/mL, or in endotoxin units (EU), where 1 ng/mL LPS is about 10 EU/mL (Al-Disi et al., 2015).

3. ASSOCIATION OF HIGH PLASMA LPS WITH AD AND RELATED DEMENTIAS

In this section we examine whether higher plasma LPS can be associated with neuroinflammation, AD, and cognitive impairment (Table 1). It has been noted that LPS and lipopolysaccharide binding protein (LBP) are implicated in increasing progressive neurodegeneration in AD (Grant & Blake, 2023).

Table 1. Cognitive test results from elevated LPS, LBP, or SFAs.

Exposure to LPS	Amount	Cognitive test result
LPS injection	0.8 ng/kg of body weight	Impairment of social cognitive processing (Moieni, Irwin, Jevtic, Breen, & Eisenberger, 2015).
LPS injection	0.4 ng/kg or 0.8 ng/kg body weight	Long-term memory performance was impaired, low dose only (Grigoleit et al., 2011).
LPS injection	0.2 ng/kg body weight	Degraded performance in declarative memory (André, et al., 2019).
LPS-induced cytokine secretion	49 ng injection of LPS	Impairments in verbal and nonverbal declarative memory functions and decreased immediate and delayed recall (Cohen et al., 2003).
LPS injection	0.2 ng/kg body weight	Significant impairment in declarative memory and word-list learning (André, et al., 2019).
LPS injection	0.8 ng/kg body weight	Negative effects on memory function (Andreasen et al., 2008).
Levels of circulating LBP	Higher	Impaired cognitive performance (André, et al., 2019).
Levels of circulating LBP	Higher	Poorer working memory/Short-term verbal memory and the digit span test (Moreno-Navarrete et al., 2017).
LPS administration	Low-dose	Impaired both immediate and delayed recall (DellaGioia & Hannestad, 2010).
Plasma LPS	Elevated	Performed worse on the post-meal cognitive test and had poorer attention during testing (Madison et al., 2020).
Cholesterol and saturated fatty acids	High intake	Increased the risk of impaired cognitive function and the development of dementia, including AD (Melo, Santos, & Ferreira, 2019).

3.1. LPS Increases Risk of Cognitive Decline and AD

Systemic markers of innate immunity, increased by LPS, are risk factors for late-onset AD. Activation of microglia precedes cerebral atrophy in AD patients. Microglial activation can be detected in around 50% of patients with mild cognitive impairment. Prospective population-based cohort studies indicate that higher serum levels of inflammatory markers can predict dementia (Arnesen, Wettergreen, You, & Fladby, 2023). LPS-induced inflammation may be significant initiators of inflammatory degeneration in AD. LPS induces neuronal cell loss by greatly increasing tumor necrosis factor-alpha (TNFα) and interleukin 1-beta (IL-1β) (Gayle et al., 2002).

Higher levels of LBP, involved in the pro-inflammatory response to LPS, were significantly associated with a 30% higher odds ratio of developing AD over 12 years in the 3-City Cohort. There was a dose-response trend between LBP levels and increased odds of developing AD. Higher levels of circulating LBP were recently found to be associated with loss of white matter integrity and impaired cognitive performance (André, et al., 2019).

LPS can infiltrate into the brain from the periphery and initiate the cascade of chronic neuroinflammatory reactions and neurodegenerative changes that can increase progression of AD (Szczechowiak, Diniz, & Leszek, 2019). High levels of plasma LPS can trigger inflammatory immune activation. Recent data clearly show that immune activation in AD can have the capacity to facilitate and trigger the pathophysiology of AD (Heppner, Ransohoff, & Becher, 2015). LBP impacted negatively on the Digit Span Test. Higher circulating LBP is associated with brain white matter damage and poorer working memory/short-term verbal memory (Moreno-Navarrete et al., 2017).

In humans, low-dose LPS administration impaired both immediate and delayed recall, but did not affect attention or executive functions. Administration of Interleukin-6 (IL-6) impaired concentration in this study (DellaGioia & Hannestad, 2010).

LPS activates microglia that damage neurons via nitric oxide, ROS, and cytokines, leading to phagocytosis of synapses and neurons (Brown, 2019). In addition, LPS expresses its neurotoxicity in the central nervous system (CNS) in part by reducing neuron-specific neurofilaments and synaptic signaling proteins, promoting neurodegeneration (Zhao, Sharfman, Jaber, & Lukiw, 2019).

Higher plasma LPS can degrade memory functioning partly due to arachidonic acid eicosanoid production, which is partially reversible with COX (cyclooxygenase) inhibitors (Yirmiya & Goshen, 2011). Microglia treated with LPS produced 14 times the prostaglandin-E2 (PGE2), and PGE2 from arachidonic acid increases IL-6 inflammation (Fiebich et al., 1998). Another study confirms that LPS can activate COX2 and increase production of ROS, for example, peroxides and superoxide (Berk et al., 2013).

3.2 LPS is Elevated in AD

Recent investigations reported higher LPS levels in grey and white matter in brains from patients with AD than in those from participants free of dementia. LPS co-localized with Amyloid-β in amyloid plaques in AD brains (André, et al., 2019). LPS is present and associated with white matter injury in AD (Arnesen et al., 2023). LPS has been reported to be higher in the AD brain and may impede the ability to repair damaged myelin (Zhan, Hakoupian, Jin, & Sharp, 2021). Another study reported three-fold higher LPS levels in the hippocampus of four AD brains compared to two age-matched control brains. There was a two-fold higher abundance of LPS in neocortical extracts from six AD brains compared to six age-matched control brains. In some advanced AD patients, the hippocampus exhibited up to a 26-fold increase in LPS concentration (André, et al., 2019). Also, plasma LPS levels were three-fold higher in 18 AD participants (mean 61 ρg/mL) than in 18 healthy controls (mean 21 ρg/mL) (André, et al., 2019). A Norwegian study also found increased levels of LPS in the hippocampus of patients with AD, compared to healthy age-matched controls (Arnesen et al., 2023).

LPS was reported to be elevated in the blood and brain of AD patients (Zhao, Jaber, & Lukiw, 2021). Another study confirmed that those with AD have plasma LPS levels three times higher than controls (Zhang et al., 2009).

Higher plasma LPS was correlated with cognitive decline and lower cognitive function. Higher plasma LPS concentration doubled the risk (OR per 0.1 ng/mL) of mild cognitive impairment in participants without dementia (Saji et al., 2022).

Subjects affected by mild cognitive impairment (MCI) had double the serum LPS levels, compared to normal aging controls. Also, those with dementia had about double the serum LPS compared to MCI patients. Serum LPS was near zero in young normal people, 150 ng/mL in normal aged people, 400 ng/mL in patients affected by MCI, and 700 ng/mL in patients affected by dementia (Sánchez-Tapia et al., 2023). Another study confirmed that levels of LPS are increased in the serum and cerebrospinal fluid of patients with AD and in the serum of patients with MCI (Saji et al., 2022).

3.3. LPS Stimulates Brain Inflammation

LPS can stimulate macrophages to produce IL-1β, IL-6, and TNFα, which go on to affect the brain. After LPS stimulation, patients with AD produced higher levels of IL-1β, IL-6, IL-10, and TNF-α than normal controls. Note that IL-10 is a compensatory anti-inflammatory cytokine (Wilson, Finch, & Cohen, 2002).

LPS can stimulate astrocytes and microglia in the CNS to secrete cytokines such as TNFα, IL-6, and interferon-gamma (IFN-γ). Microglial activation preceded the neuronal degeneration (Niehaus & Lange, 2003). Systemic inflammation evoked by LPS can induce microglial expression of IL-1β and also increase neuronal apoptosis in the brain. Thus, both central and peripheral inflammation can increase local brain inflammation and neuronal death, increasing neurodegeneration (Cunningham, Wilcockson, Campion, Lunnon, & Perry, 2005).

Higher circulating LPS levels increased TLR-4 protein expression two-fold ($p<0.05$). Higher LPS caused a significant increase in TNFα from 1 pg to 33 pg and IL-6 secretion from 2.7 ng/mL to 4.8 ng/mL. Nuclear factor-kappa-B (NFκB) is clearly involved in this increase of cytokines because a NFκB inhibitor stopped the increase of IL-6 (Creely et al., 2007).

Increases in IL-1β have been documented after LPS challenge. IL-1β can induce microglial proliferation, stimulate microglial expression of IL-6, and activate microglia. IL-1β may promote neurodegeneration through generation of reactive nitrogen species such as peroxynitrite. IL-1β also appears to be a mediator of apoptosis. Additional neurotoxic properties of IL-1β include blood-brain barrier (BBB) damage and increased amyloid-β (Wilson et al., 2002).

LPS can compromise the integrity of the BBB and contribute to early neuroinflammatory changes and AD by priming microglia and impairing amyloid clearance. Circulating LPS can activate the receptor for advanced glycation end products (RAGE) to amplify pro-inflammatory signaling and promote chronic neuroinflammation and neurodegeneration, particularly in brain regions sensitive to AD such as the hippocampus (McGrattan et al., 2019).

3.4. LPS, Neuroinflammation, and Amyloid

LPS can trigger the lipopolysaccharide receptor cluster of differentiation-14 (CD14) that interacts with fibrillar, but not with aggregated, amyloid-β peptide in AD (Eikelenboom et al., 2010). LPS, through CD14 and TLR-4, can strongly increase amyloid-β microglial activation and neurotoxicity. Thus, LPS through CD14 may significantly contribute to the overall neuroinflammatory response to amyloid peptide (Fassbender et al., 2004).

Pro-inflammatory cytokines are centrally up-regulated in regions undergoing neurodegeneration and, in the case of AD, in regions manifesting amyloid-β deposits or neurofibrillary tangles. Once the inflammatory cascade has been stimulated, cytokines can amplify their own production (Wilson et al., 2002).

One study found that neuroinflammation induced by LPS increases cognitive impairment through an increase of beta-amyloid generation (Lee et al., 2008). Amyloid plaques are co-localized with pro-inflammatory cytokines, clusters of activated microglia, and reactive astrocytes (Eikelenboom et al., 2010). Although the presence of

amyloid-β plaque is not well correlated with reduced cognition, inflammatory plaque does show a strong correlation with impaired cognition (Wilson et al., 2002).

LPS can increase amyloid-β production and accumulation and the hyperphosphorylation of tau protein (Saji et al., 2022). High plasma levels of LPS can increase the permeability of the blood-brain barrier, allowing toxic plasma components, including amyloid β and α-synuclein into the brain. LPS may also promote the production or aggregation of amyloid β, tau, and α-synuclein. LPS is found in amyloid plaques (Brown, 2019; Zhan et al., 2016).

High LPS levels may compromise BBB integrity, stimulate and sustain inflammation in the CNS and facilitate the AD pathological cascade. Inflammatory cytokines may have a direct effect on amyloid aggregation or an indirect effect via endothelial dysfunction. Increased central and systemic expression of cytokines has been reported in AD patients (Marizzoni et al., 2020).

3.5. Saturated Fatty Acids Can Raise Serum LPS and Impact Cognition

High intakes of dietary saturated fat can almost double the risk of dementia (RR = 1.9) (Kalmijn et al., 1997). Saturated fat intake promoted increases in circulating LPS levels and TLR-4 gene expression in women. Elevation of serum LPS due to a high-fat diet was dependent on the dietary levels of saturated fatty acids (SFAs) (Rohr et al., 2020). Women with elevated LPS performed worse on the post-meal cognitive test and had poorer attention during testing (Madison et al., 2020). Two of the saturated fatty acids, lauric and palmitic acids, along with LPS, increased activation of TLR-4 to increase inflammation, whereas unsaturated fatty acids did not increase the activation of TLR-4 (Meessen, Warmbrunn, Nieuwdorp, & Soeters, 2019). Note that it is possible that SFAs are unable to directly stimulate TLR-signaling without the presence of LPS (Erridge, 2011a).

The consumption of a high saturated-fat diet has been associated with increased postprandial levels of LPS and increased circulating levels of pro-inflammatory markers. LPS was increased by 60% following the consumption of a high SFA meal and the high levels of LPS lasted longer (three hours versus one hour following a low-fat meal) (André, et al., 2019). High intake of dietary cholesterol and SFAs increased the risk of impaired cognitive function and the development of dementia, including AD (Melo et al., 2019).

3.6. Injecting LPS Impairs Cognition

It has been reported that two hours after an injection of LPS (0.8 ng/kg of body weight), TNFα was raised 32-fold (5-160 pg/mL) and IL-6 was raised 68-fold (2-135 pg/mL), and this increase of inflammatory markers was associated with impairment of social cognitive processing (Moieni et al., 2015).

After injection, LPS can be measured in plasma within a few minutes. LPS is then transported to the liver for clearance. Within the first hour after LPS administration, TNFα, IFN-γ, and IL-6 appear in plasma. TNFα peaks after 90 minutes, whereas IL-6 and IFN-γ peak after 120 minutes. IL-1β peaks between 90 and 120 minutes. Compensatory, anti-inflammatory IL-10 peaks at 3 hours post injection (Andreasen et al., 2008).

In one human study, injections of LPS were either 0.4 ng/kg of body weight or 0.8 ng/kg of body weight, approximately 24 ng or 48 ng, respectively. Pro-inflammatory cytokines, such as IL-6 (up 180 pg/ml) and TNFα (up 110 pg/ml), were greatly increased by injected LPS within two hours. These two cytokines play a pivotal role in mediating cognitive impairment by transferring peripheral inflammation to the brain. Long-term memory performance was impaired selectively for emotional stimuli after administration of the lower, but not of the higher, dose of LPS. The impact on cognition may vary with type of bacterial LPS and the timing of the testing. We suggest that there may be delayed compensatory changes, such as increased anti-inflammatory IL-10, triggered by the LPS injection (Grigoleit et al., 2011).

In a human study, LPS was injected in the small amount of 0.2 ng/kg (14 ng for a 70 kg person). TNFα was doubled and IL-6 raised 700%, peaking at three hours post injection. Performance in declarative memory was worse

with increases in IL-6. Subjects with small increases in IL-6 performed better than subjects with larger increases (André, et al., 2019; Lindsay, 2022).

LPS-induced cytokine secretion has been correlated with impairments in verbal and nonverbal declarative memory functions. LPS can decrease immediate and delayed recall (Cohen et al., 2003). Another study reported a significant impairment in declarative memory until 10 hours after the injection of LPS. Additionally, word-list learning performance worsened between 4.5 hours and six hours after LPS injection (André, et al., 2019).

After LPS injection of 56 ng in humans, TNFα in plasma rose 11-fold from 10 to 110 pg/mL in two hours and IL-6 rose 20-fold from 5 to 100 pg/mL (Szczechowiak et al., 2019). The injection of 0.8 ng/kg LPS resulted in TNFα levels of approximately 100 pg/ml, with negative effects on memory function (Andreasen et al., 2008).

3.7. Injecting LPS Increases Neuroinflammation

Injection of 28 ng LPS resulted in marked activation of microglia in the brain for 3 hours as shown by PET scan (Salardini et al., 2020). It is well established that intravenous injection of as little as eight ng LPS can be sufficient to stimulate a detectable inflammatory response in humans. Injection of 60 ng evoked a 44-fold increase in TNFα from 1 to 44 pg/mL in two hours. IL-6 went up 69-fold from 2 mg/mL at baseline to 138 mg/mL in 2 hours. C-reactive protein (CRP) was elevated 52-fold from 0.34 to 18 mg/L with strong increases continuing up to 24 hours or more (Ferguson et al., 2013). After LPS injection memory functions were significantly decreased correlated with increased cytokines (Reichenberg et al., 2001).

LPS administration (1.0 ng/kg, i.v.), 60 ng for a 60 kg person, increased blood levels of inflammatory cytokines. The LPS injection also significantly increased microglial activation throughout the brain, revealed by PET scan (Sandiego et al., 2015).

4. ASSOCIATION OF HIGH CYTOKINE LEVELS WITH AD AND COGNITIVE IMPAIRMENT

Under normal conditions, low levels of brain cytokines can help hippocampal memory and neurogenesis. When activated, microglia and astrocytes can secrete high levels of pro-inflammatory cytokines, producing detrimental effects on memory, neuronal plasticity, and neurogenesis. Administration of LPS was found to impair learning and memory. In AD subjects, higher levels of IL-6 have been correlated with the severity of the dementia (Yirmiya & Goshen, 2011). The hippocampus is vulnerable to high levels of IL-1β, IL-6, and TNFα, and these cytokines may reduce synaptic plasticity and may inhibit neurogenesis (Melo et al., 2019).

High levels of inflammatory plasma IL-6 and TNFα have been significantly related to poorer memory. LPS administration produced a global decrease in memory functions, reflected by decreased immediate recall of story items, reduced delayed story recall, impaired immediate and delayed recall of figure items, and decreased performance in Word List Learning. With low dose LPS injection (.2 ng/kg), declarative memory performance was worse when there were LPS-induced increases in circulating IL-6 levels (Yirmiya & Goshen, 2011).

4.1. Excess Inflammation Increases Cognitive Decline

It has been demonstrated that higher plasma LPS can increase inflammatory cytokines. Studies have shown that excess immune activation can contribute to and drive AD pathogenesis. Inflammation in AD primarily concerns the innate immune system. Inflammatory IL-1β, IL-6, and TNFα are up-regulated in the brains and cerebrospinal fluid of humans with AD (Szczechowiak et al., 2019).

In three hundred community-dwelling subjects with mild to severe Alzheimer disease, high levels of TNFα were associated with a four-fold increase in the rate of cognitive decline. In contrast, subjects who had low levels of serum TNFα throughout the study showed no cognitive decline over a six-month period. It can be hypothesized that in AD, acute systemic inflammation associated with increased TNFα can lead to increased cognitive decline (Holmes et al., 2009).

There is a growing appreciation of the role of cytokine-mediated inflammation in neurodegenerative diseases such as AD and vascular dementia. Peripheral cytokines enter the blood-brain barrier directly via active transport. IL-1β, IL-6, and TNFα are typically considered proinflammatory, whereas IL-4, IL-10, and IL-13 are typically considered anti-inflammatory. There is abundant evidence that inflammatory mechanisms within the central nervous system contribute to cognitive impairment via cytokine-mediated interactions between neurons and glial cells (Wilson et al., 2002). Higher serum IL-6 Level can predict the development of disability in older persons and can increase their risk of dementia (Ferrucci et al., 1999).

High levels of serum IL-6 have been correlated with lower cognitive functioning and can raise the risk of subsequent cognitive decline (Wilson et al., 2002). Clinical observations in humans suggest that there is a cytokine-mediated decrease in memory functions as a consequence of acute peripheral inflammation. Mean reaction time was significantly reduced by 27.6 milliseconds after endotoxin administration exclusively in the high-dose group (Grigoleit et al., 2011).

Acute systemic inflammation can elicit a negative impact on central nervous system function, inducing neuropathological changes that can accelerate the onset of neurodegenerative disease. In a cohort of 275 AD patients across a six-month period, elevated serum TNFα was significantly correlated with accelerated cognitive decline. Conversely, those patients with low serum TNFα showed stable cognitive function during this period. Elevated serum IL-1β was significantly associated with increased cognitive decline across a two-month period (Cunningham, 2013).

Plasma levels of inflammatory proteins have been found to be increased before the clinical onset of dementia, indicating that they may be a contributing factor. When IL-6 was higher in the Rotterdam Study, risk of AD and dementia was elevated by 28% and risk of vascular dementia was elevated by 26%, per standard deviation of IL-6 (Engelhart et al., 2004).

Cytokine-mediated inflammation is likely to exacerbate progression of AD in association with factors such as reactive oxygen damage. Subjects with late-stage dementia have been shown to have higher levels of IL-6 in the entorhinal cortex and superior temporal gyrus at autopsy (Wilson et al., 2002). Systemic and CNS inflammation, including heightened IL-1β, TNFα, and interferon-beta, can induce cognitive changes and accelerate neurodegenerative disease (Cunningham et al., 2009).

Cytokines can activate glial cells and, conversely, glial cells can produce cytokines when activated. Specific combinations of cytokines can induce dose-dependent neuronal injury, so cytokines can act as direct contributors to neuronal injury upon release by activated microglia or astrocytes. In addition, cytokines can activate microglia to produce free radicals. The debris created by neuronal damage may further activate microglia and astrocytes, leading to a vicious cycle of damage (Wilson et al., 2002).

4.2. Increased IL-6 and Activities of Daily Living

Higher circulating levels of IL-6 predict disability onset in older persons. Participants in the highest IL-6 tertile were 1.76 times more likely to develop mobility-disability and 1.62 times more likely to develop mobility plus activities of daily living (ADL)-disability compared with the lowest IL-6 tertile (Ferrucci et al., 1999).

Cross-sectional studies have reported an association between increases in IL-6 and functional status as indicated by ADL or instrumental activities of daily living (IADL) measures. IL-6 levels are correlated with subsequent development of disability in ADLs/IADLs (Cohen, Pieper, Harris, Rao, & Currie, 1997). Interleukin-6 and C-reactive protein play an important role in the pathogenesis of dementia. Higher levels of IL-6 predict a decline in the activities of daily living (Ferrucci et al., 1999) Higher levels of LPS almost doubled the impairment of IADL from 27% to 50% (Saji et al., 2022).

4.3. Autopsy Findings of Higher Cytokines in AD

Activated microglia and inflammation-related mediators have been found in the cerebral neocortex of autopsied patients with early AD pathology (Eikelenboom et al., 2010). Increased levels of IL-1β, IL-6, or TNFα have been found in peripheral blood or autopsy specimens of patients with mild to moderate late-onset AD (Wilson et al., 2002).

A study on autopsied AD brains showed the presence of LPS in brain lysates from the hippocampus and superior temporal lobe neocortex. LPS levels in AD brains varied from two-fold increases in the neocortex to three-fold increases in the hippocampus, compared to age-matched control brains. Some hippocampal samples from advanced AD cases exhibited up to a 26-fold increase in LPS over age-matched controls. The hippocampus has been found to be the area of the brain that developed the earliest and most profound neuropathology in AD (Zhao, Jaber, & Lukiw, 2017).

4.4. Cytokine Therapy Can Impair Cognition

Normal individuals who receive systemic cytokine therapy such as interferon-alpha (IFN-α), IL-2, and TNFα at therapeutic doses frequently describe impaired thinking processes (Licinio, Kling, & Hauser, 1998). Chronic peripheral administration of IL-2 has been associated with hippocampal neurodegeneration and suppression of hippocampal long-term potentiation, leading to impaired memory performance. Therapeutic administration of IFN-gamma in humans can result in an array of CNS side effects including confusion, psychomotor slowing, thought blockade, subjective memory loss, impaired motor and executive functioning, and even sustained slowing of reaction times at higher doses (Wilson et al., 2002).

5. LPS CAN REPRESENT A RISK FACTOR FOR ATHEROSCLEROSIS AND REDUCED BRAIN PERFUSION

Cytokines have prothrombotic effects and can influence many steps of the atherogenic process. IL-1β, IFNγ, and TNFα can induce smooth-muscle degeneration by apoptosis, whereas TNFα, IL-1β, or IL-6 may promote cellular adherence to endothelial cells (Arvin, Neville, Barone, & Feuerstein, 1996).

The atherogenic and prothrombotic effects of cytokines may directly influence vascular dementia risk. By influencing the response to ischemia, cytokines may determine the point at which multiple serial ischemic insults overcome an individual's cognitive reserve threshold. In addition, IL-1β and TNFα are known to modulate endothelial functions that govern the formation and stability of blood clots. Cytokines can directly influence the coagulation cascade. IL-1β, IL-2, IL-6, and TNFα can increase thrombosis (Wilson et al., 2002).

5.1. Brain Perfusion

Brain perfusion of blood is vital to supply glucose and oxygen to brain neurons. High cytokine levels can exacerbate the cerebral hypoperfusion and blood–brain barrier leakiness that are associated with AD and vascular dementia (Asby, Boche, Allan, Love, & Miners, 2021). Ninety minutes after LPS injection at a dose of 2 ng/kg body weight in healthy young volunteers, it has been reported that cerebral blood flow was reduced by 24% (Møller et al., 2002).

5.2. Atheroslerosis, LPS, and LBP

Upon stimulation with LPS, macrophages and neutrophils release thromboxane A2, which can constrict blood vessels and thicken blood. The presence of LPS and proinflammatory cytokines can change endothelial cells to promote a procoagulant profile. This may increase atherosclerosis and reduce brain perfusion (Andreasen et al., 2008). High plasma LPS levels are associated with major adverse cardiovascular events, possibly by increasing platelet activation (Pastori et al., 2017).

When college students ate a high-fat meal (thin crust cheese pizza), in addition to raising LPS 65 times, there were increases in oxidized LDL uptake and adhesion molecule expression in monocytes. Consumption of a high-fat meal also increased the potential of monocytes to become foam cells. Monocyte-derived foam cells are the predominant component of arterial plaques in the early stages of atherosclerosis (Henning, Venable, Vingren, Hill, & McFarlin, 2018). Serum LPS was near zero in young normal people and median LPS levels in hundreds of men and women ages 50-79 was 14.3 pg/mL. Risk of atherosclerosis rose with higher LPS levels (Wiedermann et al., 1999). Plasma levels of LPS in patients affected by dementia was 700 ng/mL (Sánchez-Tapia et al., 2023).

5.2.1. LPS and LBP Damage Cerebral Arteries

LPS binds to transmembrane receptors within the toll-like receptor family, initiating a cascade of cytokines and other inflammatory mediators, followed by vascular injury (Funari & Testai, 2008). LPS-induced inflammation via TLR-4 (which is expressed in atherosclerotic plaque) has been shown to play an important role in the pathogenesis of atherosclerosis (Ghanim et al., 2009). TNFα and IL-1β activate blood coagulation and stimulate the expression of adhesion molecules on endothelial cells, possibly reducing brain perfusion (Andreasen et al., 2008).

LBP can be used as a marker to indicate activation of an inflammatory response due to plasma exposure to LPS. LBP was reported as a factor related to atherosclerosis. Systemic inflammation, triggered by dietary LPS, has been associated with increased plasma concentrations of pro-inflammatory cytokines, and is a risk factor for atherosclerosis (Laugerette et al., 2014).

There was a strong correlation between serum LBP and coronary artery disease. The proinflammatory action of LBP bound to LPS might be an important contributor to the progression of cardiovascular incidents and associated mortality. In those with more severe coronary artery disease, circulating LBP was higher. Circulating LBP was found to be increased in people with elevated carotid plaque. Interestingly, LBP deposits were found inside atherosclerotic plaque. There was a consistent association between serum LBP and the carotid intima media thickness, a widely used atherosclerosis marker (Serrano et al., 2013).

5.3. BBB Damage and Cytokines

The binding of cytokines to endothelial receptors in the brain vessels may stimulate the release of other mediators, such as endothelial cell adhesion molecules, chemokines, nitric oxide, and prostaglandins, which may lead to impairment of BBB integrity (Wilson et al., 2002).

High levels of TNFα and IL-1β can promote the recruitment of inflammatory cells, their adherence to brain endothelial cells, and enhanced vascular permeability of the BBB. Cytokines can increase atherosclerosis and smooth muscle apoptosis of endothelial cells (Arvin et al., 1996). The barrier function of the BBB decreases with age, in AD, and in response to elevated levels of TNFα, IL-1β, and IL-6 (Lindsay, 2022).

6. LPS IN FOOD AND DIETS

6.1. Cooking and LPS

LPS was found to be highly resistant to typical cooking times and temperatures (Erridge, 2011a). LPS has a strong thermal stability, and food processing only partially removes LPS. Note that the amount of LPS triples in meat during 10 days of refrigerated storage (Jay, Margitic, Shereda, & Covington, 1979). LPS in meat may be reduced as much as 60% by cooking, but boiling LPS in saline for up to 1 hour resulted in limited or no reduction in the biological activity of LPS (Erridge, 2011a).

6.2. LPS in Milk

Milk was analyzed in five European countries and contained an average LPS content of 50 ng/mL, although values varied 10-fold. Thus, an average 8 fluid ounce cup of milk (240 mL) was found to contain 12,000 ng of LPS

(Gehring et al., 2008). Another study found that urban raw milk contained 18,000 ng LPS per cup and that LPS in eggs may have 27 times more endotoxin than red meat (Venter, 2010). Although not all of the LPS in food goes into plasma, note that an injection of as little as 60 ng of LPS raised TNFα 44-fold and IL-6 69-fold in 2 hours (Ferguson et al., 2013).

In a milk powder survey, infant formula studies from seven countries and 31 brands found LPS levels ranging from 4 ng/g to 5500 ng/g in the milk powder formula. The average infant intake of LPS per day from 100 g milk powder was estimated to be about 280,000 ng/day (Hansen, Mikkelsen, & Møller-Madsen, 1982). The most common level of LPS found in skim milk was 50-100 ng/ml, or about 18,000 ng per cup—more than a thousand times more than the 10 or less ng of LPS in the entire upper intestine (the jejunum) (Wu et al., 2021).

6.3. LPS in Meat and Processed Foods

A recent study found that the largest dietary risk factor for AD was meat consumption (Grant & Blake, 2023). The ingestion of dietary LPS can result in systemic cytokine release and inflammation. Much of the dietary LPS translocates into the systemic circulation in a biologically active form (Erridge, 2011a). LPS levels were found to be highest in beef, pork, and turkey.

A study on toll-like receptors indicate that a 400 g processed food meal may contain an average of about 200,000 ng LPS. Examples of processed food servings are included in Table 2. By comparison, intravenous injection of as little as 8 ng LPS is able to stimulate a detectable inflammatory response in man (Ferguson et al., 2013). This suggests that the quantity of LPS in a processed food meal can be up to 25,000-fold higher than is required to stimulate inflammation, if given by injection (Table 2) (Faraj, 2017).

Table 2. LPS per serving in food, References are in the text.

Food	ng/g of LPS	Serving size g	LPS per serving in ng
Macaroni and cheese	6,500	340	2,200,000
Minced turkey	7800	230	1,800,000
Cheese and onion rolls	17,000	74	1,300,000
Minced pork	10,000	110	1,100,000
Minced beef	7000	98	690,000
Pork sausage rolls	4,200	2 rolls 120	520,000
Turkey	300	230	510,000
Hamburger patty	3090	98	300,000
Infant formula milk powder	2800	100	280,000 (Hansen et al., 1982)
Lobster	1200	145	170,000 (Prester, Orct, Macan, Vukušić, & Kipčić, 2010)
Pork	1100	110	120,000
Spaghetti Bolognese	220	400	90,000
Minced beef and onion pie	330	310	69,000
Skim milk, one cup	75 ng/ml	240	18,000 (Wu et al., 2021)
Milk, one cup	50	240	12,000 (Gehring et al., 2008)

A serving of lobster of 145 g was found to contain 170,000 ng of LPS (Prester et al., 2010). Ground beef was examined for LPS content in 84 samples and the average content of LPS in the ground beef was 3100 ng/g. A typical 98 g hamburger patty was found to contain 303,000 ng of LPS. Please see Table 2 for quantities of LPS in pork, minced pork, turkey, minced turkey, minced beef, and other foods. Foods containing minced meat and cheese contained a particularly high abundance of LPS compared with the rest of the foods examined (Erridge, 2011a).

Increased processed meat intake was shown to be associated with a significant increase in risk of elevated inflammation and cardiovascular disease. By contrast, the Mediterranean dietary pattern is defined in part by relatively low intake of pre-packaged 'ready meals' and processed meat, and is likely a lower LPS diet for these

reasons (Herieka, Faraj, & Erridge, 2016). Unprocessed fruit, vegetables, grains, and potato are quite low in LPS (Figure 2) (Erridge, 2011a).
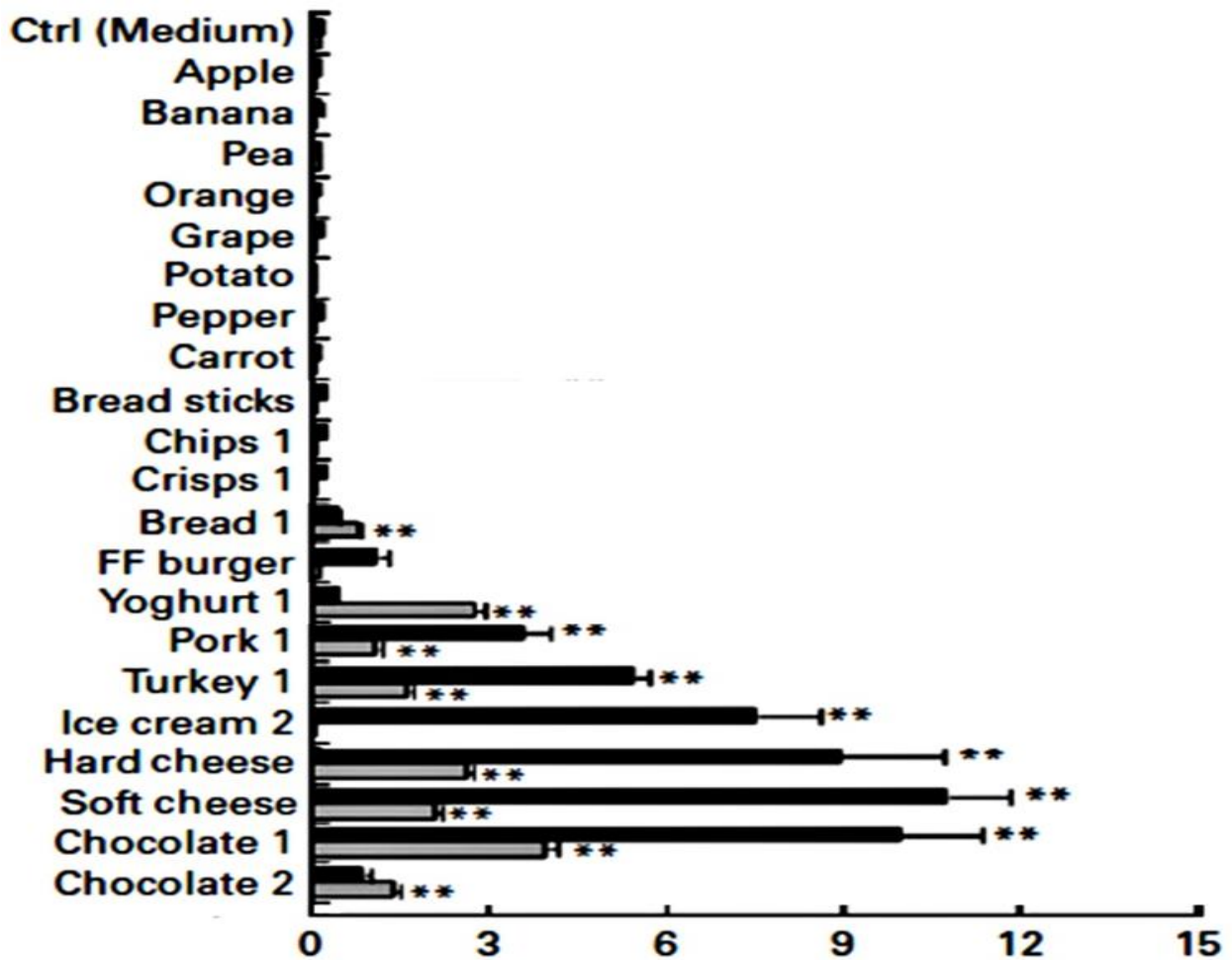

Figure 2. LPS-triggered cytokines in food samples. Dark bars are soluble, grey insoluble.
Note: **Mean values were significantly different when compared with medium alone (P, 0·001 by ANOVA with Dunnett's test).
Source: Erridge (2011a).

Restricting dietary LPS could reduce plasma LPS levels to significantly reduce inflammation (Brown, 2017). Those who ate more fruit had 34% less circulating LPS. Those who ate more legumes had 20% less circulating LPS in a large prospective study with 912 participants. Adherence to the Mediterranean diet was also significantly associated with lower circulating LPS (Baratta et al., 2020) when compared to a Western Diet (André, et al., 2019; Pastori et al., 2017).

6.4. LPS in Diets

Dietary modification can lower plasma LPS (Estadella et al., 2013). Placing eight healthy subjects on a Western-style diet for one month in a controlled metabolic ward induced a 71% increase in plasma levels of LPS activity, whereas a prudent-style diet reduced levels by 31% (Pendyala, Walker, & Holt, 2012). A high fat diet triggered inflammation and cytokines independently of LPS (Mo, Huang, Burnett, Rutledge, & Hwang, 2020). If each meal contains high levels of LPS that stimulates inflammation for about four hours, then over 12 hours per day may be spent in an inflammatory postprandial state (Meessen et al., 2019).

A study of 668 participants found that healthy dietary choices, such as consumption of fresh vegetables, fruits, and berries may be associated with positive health outcomes by reducing systemic endotoxemia. Cheese highly

raised plasma LPS in this study (Ahola et al., 2017). Possibly related was a significant association between adherence to the Mediterranean diet and lower rates of cognitive impairment (Pastori et al., 2017).

Plasma LPS level is highest with a Western diet high in meat. Mediterranean and complex carbohydrate diets are moderately lower in LPS. A "prudent" diet containing fruit and vegetables, but low in cookies, had the least plasma LPS (André et al., 2021). Meals with plenty of fiber and fruit do not induce inflammation, do not increase the expression of TLR-4, and do not raise plasma concentrations of LPS or LBP (Ghanim et al., 2009).

Dietary patterns with high intakes of vegetables and fruits, and low consumption of meat have been correlated with a healthier microbiota in the colon, which can be beneficial for the brain by limiting LPS translocation into plasma. However, overconsumption of foods rich in simple carbohydrates, saturated and trans fatty acids, red meat, processed meat, organ meats, and chips, can have a proinflammatory influence on the AD patient's brain (Szczechowiak et al., 2019).

6.5. LPS after a Test Meal

Serum LPS significantly increased at each postprandial time point (compared to before a meal) of thin crust cheese pizza, with peak plasma LPS 65-fold at five hours postprandial (P=0.001) (Henning et al., 2018).

Meals with a high LPS and fat content have been implicated as a trigger of postprandial inflammation through the activation of NFkB (Al-Disi et al., 2015; Hawkesworth et al., 2013). One study used a healthy American Heart Association meal compared to an equicaloric high-fat meal with egg sausage muffin with hash browns. The high-fat meal induced inflammation through LPS and TLR-4, increased TNFα, IL-6, and increased oxidative stress for two to three hours after the meal. Plasma LPS went up 45% and NFkB increased 72% with the high fat meal only. The healthier meal did not raise LPS, TLR-4, or cytokines (Ghanim et al., 2009). One study compared isocaloric meals (300 kcal) from a glucose drink, orange juice, or dairy cream among 42 healthy adults. Only dairy cream consumption increased postprandial plasma LPS levels (André, et al., 2019).

Ingestion of LPS and saturated fat in 100 ml heavy whipping cream promoted LPS-mediated inflammation. Two hours after the whipping cream, plasma LPS increased 83%. 100 mL of heavy cream also raised TNFα 11% after two hours. LPS area under the curve (AUC) went up 70-270 in obese individuals. TNFα plasma LPS levels went up 23-40 incremental AUC (González, Considine, Abdelhadi, & Acton, 2019).

Milk fat, 40 g, with breakfast, more than doubled plasma LPS. AUC plasma IL-6 levels doubled when consuming 40 g compared to 10 g milk fat with breakfast. Plasma LPS went up three to five-fold after three hours in the high milk fat group. In obese subjects, plasma LPS went from 1 to 17.5 ng/mL (1.8-1.9 ng/mL is normal) (Vors et al., 2015). Another study looked at people with a low-fat diet (largely excluding high-fat meat and cheese) and serum LPS levels were much lower, ranging from 0 to 0.2 ng/mL (Rohr et al., 2020).

Circulating LPS after a high fat meal was raised at least 150% after four hours (Harte et al., 2012). Serum LPS increased by 60% following the consumption of foods high in saturated fatty acids, lasting for 3 hours post meal (Lyte, Gabler, & Hollis, 2016).

7. DIETARY LPS ENTERS THE BLOODSTREAM AND TRIGGERS INFLAMMATION

LPS in food can trigger systemic cytokine release and inflammation. Some of the LPS in food gets into systemic circulation in a biologically active form (Erridge, 2011a).

LPS absorption is largely a postprandial phenomenon, but can also be from chronic dysbiosis (imbalanced gut bacteria) or oral infection (Laugerette et al., 2014). Once LPS-laden chylomicrons are in the bloodstream, LPS are taken up by LPS binding protein (LBP). LBP is produced by the liver and present in the blood at concentrations of approximately 2-20 µg/mL. LBP is transferred to the receptor CD14. CD14 is expressed on the plasma membrane of various cell types, such as monocytes, macrophages, and human intestinal epithelial cell lines. Besides this membrane-bound state, CD14 is also found in a circulating soluble form (sCD14). sCD14 is involved in the

bioactivity of circulating LPS and can be considered as an accurate marker of LPS in plasma. Both membrane-bound and soluble forms of CD14 can bind the LPS-LBP complex and mediate signal transduction, including the activation of the transcription factor nuclear factor-kappa-B (NFκB) via TLR-4. This signaling cascade results in the release of pro-inflammatory cytokines such as Interleukin IL-1β, IL-6 and TNFα. Intestinal cells are able to produce, express, and release molecules of LBP, CD14, and TLR-4 (Laugerette et al., 2014; Laugerette et al., 2011).

Pro-inflammatory LPS co-absorbs with dietary lipids. This explains how consumption of milk fat increases intestinal absorption of LPS. LPS is then incorporated into chylomicrons, enters the bloodstream, and consequently contributes to postprandial endotoxemia and inflammation. LPS levels in chylomicrons increased, spiking at three hours after a high milk fat (40 g) meal. Emulsified milk fat triggered an early and sharp increase in chylomicron-endotoxemia at 60 min after ingestion (Vors et al., 2017). Plasma LPS resulted in a robust cytokine response (White et al., 2018).

7.1. Colonic Sources of Plasma LPS

High-fat diets are associated with a reduction in intestinal bacterial diversity, increased colonic membrane permeability, increased numbers of Gram-negative bacteria, and increased LPS translocation to plasma. This can lead to the production of low-intensity systemic inflammation. In contrast to the immediate (1-4 hours) raised serum LPS from LPS in food, this colonic dysbiosis represents a chronic condition (Candido, Alfenas, & Bressan, 2018). LPS from periodontitis can also enter the gut and become absorbed into the bloodstream. Even saliva of healthy subjects has been measured to contain a median of 7 ng/ml of LPS (Erridge, 2011c).

Exposure to a high-fat diet increases systemic LPS concentration. LPS leakage from the colon is determined by the integrity of the colonic epithelial barrier, which may also be less effective with a high-fat diet (Hawkesworth et al., 2013). Five days of a high saturated fat diet in healthy participants resulted in an approximately two-fold increase in fasting serum LPS concentrations (Bowser et al., 2020). Another high-fat diet study found that bile acid synthesis was increased 10-fold and that these bile acids induced intestinal hyperpermeability. Note that bile acids do not reach the colon fast enough to impact the release of LPS from the colon in one to four hours (Rohr et al., 2020).

A high-fat diet increased colonic LPS biosynthesis. The high-fat diet was also associated with raised colonic inflammatory arachidonic acid levels, leading to elevated plasma proinflammatory factors such as leukotriene-4 and prostaglandin-2 (Wan et al., 2019).

Saturated fats, but not unsaturated fats, may lead to damage to the colonic mucus barrier (Michalski, Le Barz, & Vors, 2021). Normally, the intestinal epithelium acts as a continuous barrier to avoid LPS translocation into the plasma (Lakhan & Kirchgessner, 2010). When high fat meals are eaten regularly, this may increase LPS production in the large intestine and damage the intestinal barrier to allow more LPS to enter the bloodstream (André, et al., 2019). However, this is a slower and longer-term process compared to food-borne LPS absorption. It is unlikely that food ingested could have an impact on colonic LPS absorption in only a few hours. The fastest intestinal transit time recorded in 1000 tests was 14 hours with 24-48 hours being much more common (Burkitt, Walker, & Painter, 1972). Hence, the postprandial elevation of plasma LPS is unlikely to come from colonic sources.

7.2. Intestinal Microbiota Versus LPS in Food

The small intestine is likely to be the primary site of LPS absorption after a fatty meal. Only low levels of endogenous LPS are present in the small intestine due to the very limited Gram-negative bacteria present in this part of the gut (Erridge, 2011b).

LPS is fat-soluble and is absorbed in a manner similar to that of the other fat-soluble nutrients via incorporation into chylomicrons with dietary fat in the small intestine (but not the large intestine). LPS leaking from the large intestine enters the portal venous system, proceeding directly to the liver, which removes LPS from

the blood with great efficiency. By contrast, dietary LPS co-absorbed with dietary fat passes first into the lymphatic system and then through the thoracic duct and into the blood, thereby avoiding the first-pass clearance by the liver. Thus, the small intestine, rather than the large intestine, is likely to be the major site of postprandial LPS absorption in the body (Erridge, 2011c).

It has been estimated that the entire digestive tract may contain one gram or more of LPS (Erridge, 2011a; Ferguson et al., 2013; Laugerette et al., 2011). The large intestine has a high density of bacteria with between 1010 to 1012 colony-forming units (CFU)/mL (Hawkesworth et al., 2013; Kastl Jr, Terry, Wu, & Albenberg, 2020).

The small intestine is a harsh environment for microbial life, owing to the short transit time, the oxygen-rich environment, the presence of antimicrobial peptides produced by Paneth cells, and the influx of digestive enzymes, bile, and food substrates (Kastl Jr et al., 2020). The jejunum is the upper part of the small intestine where chylomicrons containing food-borne LPS are formed. It is estimated that the jejunum has a bacterial density of 100-4 CFU/mL (Erridge, 2011c; Laugerette et al., 2011). Unlike that of the large intestine, the microbiota of the jejunum consists mainly of Gram-positive bacteria, and the numbers of Gram-negative bacteria are low. The total LPS content of the microbiota of the small intestine seems likely to be low and is estimated to be only 1-10 nanograms of LPS. The low numbers of bacteria in the small intestine therefore suggest that the majority of the LPS present in the small intestine is likely to be derived from food and possibly from oral microbiota, rather than from products of bacteria endogenous to the small intestine (Erridge, 2011b).

With only 1-10 nanograms of LPS in the jejunum, even if much of the LPS were absorbed, it would barely affect blood LPS or inflammation. The LPS content of several commonly consumed processed foods can reach concentrations that are thousands of fold-higher than those normally present in the entire healthy small intestine (Erridge, 2011c). For comparison, about 48 ng of LPS were injected in humans to provoke increased cytokines and decreases in memory performance (Cohen et al., 2003; Reichenberg et al., 2001). Pasteurized skim milk contains more than a thousand times more than the 10 or less ng of LPS in the entire jejunum (Hansen et al., 1982).

The duodenum and jejunum are tasked with facilitating most of the nutrient assimilation and absorption (Kastl Jr et al., 2020). We have given several examples of high levels of LPS and resulting cytokines in blood 1-4 hours after eating certain high fat meals. A high-fat diet increases chylomicron formation. Chylomicrons have high affinity for LPS and transport postprandial fat along with LPS (Ghoshal, Witta, Zhong, De Villiers, & Eckhardt, 2009; Moreira, Texeira, Ferreira, Peluzio, & Alfenas, 2012).

Fats and LPS from a meal can be absorbed in the jejunum and delivered to the bloodstream via chylomicron formation and transport. There is a transient increase of LPS blood levels following ingestion of high-fat meals (Michalski et al., 2021). As we have seen, there is not enough microbiota-produced LPS present in the jejunum to elevate LPS and cytokines to the extent observed. One to four hours after a meal is not enough time for the fatty food to reach the colon and release the LPS therein. Therefore, the postprandial efflux of LPS into the bloodstream must come from the food eaten (with the addition of periodontal-derived LPS).

7.3. Transport of LPS into the Blood by Saturated Fats and Chylomicrons

LPS and saturated fatty acids have been shown to be transported by chylomicrons, suggesting a mechanism through which a high fat diet may increase LPS levels (Hawkesworth et al., 2013). Therefore, consuming a diet high in saturated fat can increase the risk of elevated plasma LPS. Saturated fat efficiently transports LPS from the gut lumen into the bloodstream (Madison et al., 2020). An increase in postprandial plasma LPS concentration was observed in healthy adults on high saturated fat diets, in contrast to subjects who received diets high in polyunsaturated fats. Dietary LPS can be incorporated into micelles, absorbed, and added to chylomicrons to increase plasma LPS. Saturated fats along with LPS can directly stimulate TLR-4 and increase inflammation (Candido et al., 2018).

7.4. High-Fat Diets Can Increase Endotoxemia

A high-fat diet can result in increased endotoxemia and inflammation due to LPS absorption from the jejunum. The inflammatory response to the high-fat meal is characterized by an increase of the pro-inflammatory cytokines IL-6 and TNFα in plasma. It has been reported that a high-fat meal is more able to enhance these inflammatory cytokines compared to a high carbohydrate meal (Laugerette et al., 2011). A high-fat diet can have a negative effect on gut microbiota, intestinal permeability and metabolic endotoxemia (Moreira et al., 2012). Chylomicrons promote intestinal absorption of lipopolysaccharides (Ghoshal et al., 2009). In a large sample of healthy men, a link was found between fatty food intake and plasma LPS (Amar et al., 2008). Plasma LPS increased significantly (P <0.05) by about 50% after a high-fat meal (Erridge, Attina, Spickett, & Webb, 2007). The ingestion of a single high-fat meal can mediate systemic increases of a wide range of inflammatory factors with noted activation of NFkB. LPS from a high-fat meal may trigger the inflammatory cascade within 1-4 hours (Lindsay, 2022).

8. CONCLUSIONS

Reducing or eliminating foods with high levels of LPS, such as processed meat and cheese, has the potential to reduce neuroinflammation. This can represent an alternative, novel technique to reduce the risk of cognitive impairment and AD progression. When brain inflammation is contributing to cognitive impairment, we hypothesize that cognition may improve or stabilize through a reduction of neuroinflammation. We have shown that, although colonic LPS may increase plasma LPS, the large postprandial increase of LPS is due to consuming LPS in food. Dietary LPS, found in certain foods, is absorbed into enterocytes and packaged into chylomicrons, which enter the bloodstream. Once in the bloodstream, LPS triggers the release of inflammatory cytokines within three hours. LPS increases cytokines via LBP, which binds to CD14, which triggers TLR-4, which in turn activates NFκB. NFκB increases cytokines, including interleukin-1-beta, interleukin-6, and tumor necrosis factor-alpha. Increases of inflammatory cytokines of over 60-fold have been measured after consuming LPS-rich food. These cytokines can enter the brain via active transport and induce microglial activation and a cascade of inflammatory damage in the brain, including loss of synapses and neurons. Therefore, elevated inflammation in the brain can contribute to cognitive impairment and increases the risk of cognitive damage. LPS and inflammatory cytokines are higher in Alzheimer's disease, both in plasma and in the central nervous system. We propose that a dietary reduction of LPS could both reduce risk and slow the progression of cognitive decline including Alzheimer's disease. More studies are needed to determine the benefits of a low LPS diet on those with cognitive impairment, mixed dementia, and AD.

Abbreviations:

ADL: Activities of daily living, AD: Alzheimer's disease, AUC: Area under the curve, BBB: Blood-brain barrier, CNS: Central nervous system, CD14: Cluster of differentiation-14, MCI: Mild cognitive impairment, CFU: Colony-forming units, COX: cyclooxygenase, CRP: C-reactive protein, EU: Endotoxin units, NFκB: Nuclear factor-kappa-B, IADL: Instrumental activities of daily living, IFN-α: Interferon-alpha, IFN-γ: Interferon-gamma, IL-1β: Interleukin 1-beta, IL-6: Interleukin-6, LPS: Lipopolysaccharide, LBP: Lipopolysaccharide binding protein, PGE2: Prostaglandin-E2, ROS: Reactive oxygen species, RAGE: Receptor for advanced glycation end-products, SFAs: Saturated fatty acids, sCD14: Soluble CD14, TLR-4: Toll-like receptor-4, TNFα: Tumor necrosis factor-alpha.

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