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Original Article

Neuroinflammation, Nuclear Factor kappa B and Memory Impairment Induced by Lipopolysaccharides

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Abstract:

Inflammatory signaling is one of the many cellular signaling channels that are regulated by the transcription factor Nuclear Factor kappa B (NF-κB). In mammals, Gram-negative bacteria's cell wall contains a chemical called lipopolysaccharide (LPS), which is commonly used to induce inflammation of the nervous system. LPS can trigger NF-κB, leading to an inflammatory response. This stimulation is part of the body's defense mechanism, in contrast to bacterial infection, but can also contribute to chronic inflammation if not regulated. So, LPS increases the expression of interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor (TNF-α) via attaching to immune cells, as a result of stimulating NF κB. Following the production of cytokines, the central nervous system (CNS)'s microglia and macrophages also generate these cytokines, which guide neuronal substrates and cause inflammation inside neurons. In addition to increasing amyloid precursor protein (APP) expression and the manufacture of amyloid plaques, which cause Alzheimer's disease, these cytokines can also increase β-secretase mRNA, protein, and enzymatic activity.

Keywords:

Lipopolysaccharide; Neuroinflammation; Nuclear factor kappa B; Alzheimer's disease.

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Introduction:

Two membranes make up gram-negative bacteria: the inner membrane (IM), which encloses the components of cytoplasm, and the outer membrane (OM), which splits the cell from its atmosphere. These sheaths border the periplasm, a fluid cellular compartment that houses the peptidoglycan cell wall **(Bertani and Ruizi, 2019).**

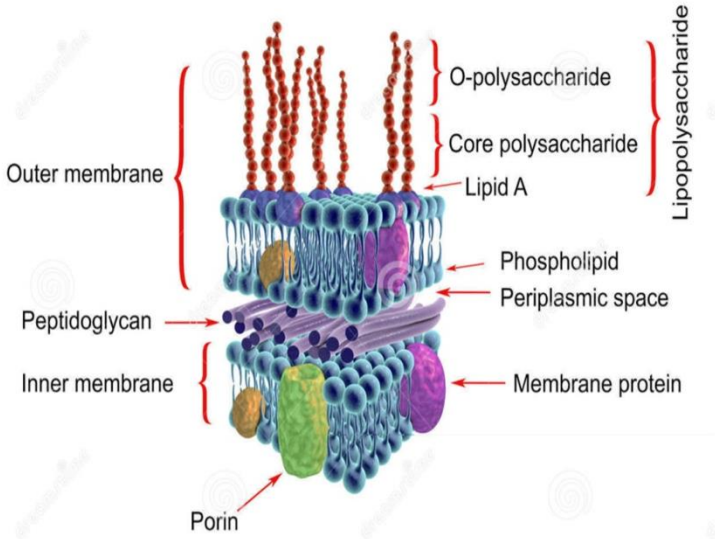

Figure 1. Structure of Gram-negative bacteria (Bertani and Ruzi, 2014).

The outer membrane mainly protects gram-negative bacteria from environmental threats. The OM of most gram-negative bacteria is essentially not a phospholipid bilayer, in contrast to many other biological membranes. It has an unequal outer membrane, with lipopolysaccharide molecules in the external booklet and phospholipids in the internal booklet **(Bertani and Ruizi, 2019).**

A glycolipid called lipopolysaccharide (LPS) has been thoroughly investigated as a bacterial surface substance. LPS has several purposes in gram-negative bacteria, but its main job is to be an essential structural element of the external sheath (OM) **(Zhang et al., 2013).** Due to the ability to convert the external sheath into a highly operative penetrability barrier, Gram-negative bacteria exhibit natural resistance to numerous antimicrobial agents. This contrasts with small, hydrophobic compounds that typically permeate phospholipid bilayers.

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Additionally, LPS plays a decisive role in bacterial-host relations by modifying the congregation's resistant response **(Bertani and Ruzi, 2019)**.

Structure of LPS:

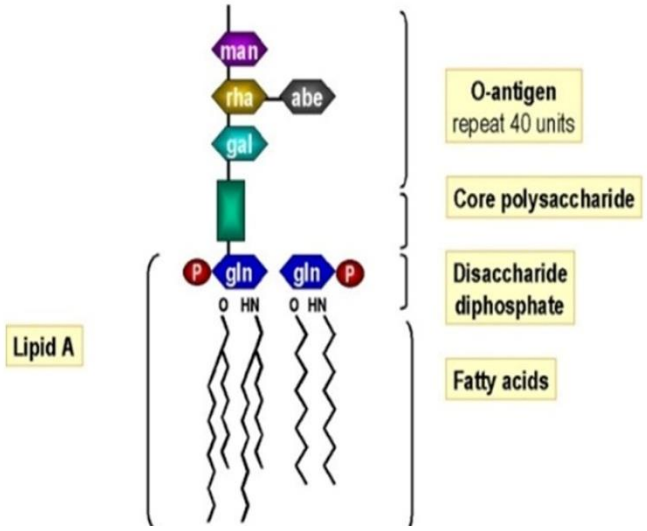

Figure 2. Structure of LPS (Sandeh et al., 2021)

Lipopolysaccharide (LPS), a huge glycolipid, is collected of three mechanical components: the O antigen, lipid A, and the core oligosaccharide. Lipid A, constitutes the hydrophobic portion of the molecule and forms the external booklet of the outer membrane. The core oligosaccharide, a non-repeating sugar chain, is committed to the glucosamine in lipid A **(Raetz and Whitfield, 2002).** The O antigen is a long polysaccharide that is involved to the core oligosaccharide and consists of a recapping oligosaccharide with two to eight sugars **(Hong et al., 2018).**

Function of LPS:

Even though various bacteria have distinct lipopolysaccharide (LPS) structures, LPS always covers a significant area of the cell outward and creates a penetrability barrier that keeps dangerous chemicals like bile salts and antibiotics from entering **(Carpenter et al., 2016).** Since The principal bacterial element that the crowd resistant system comes into contact with is LPS, which frequently contributes significantly to the pathogenicity of bacteria (**Scott et al., 2017).**

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Many bacterial pathogens include lipopolysaccharide (LPS) on their surface. Its presence triggers a strong immunological response in the host **(Sassi et al., 2010).** The host may become poisoned by this reaction if it is severe enough. The term "endotoxin" has been used historically to refer to LPS because of the cell-associated (endo) toxicity that is seen in a lot of gram-negative things.

The immune system predominantly responds to the lipid A structure, the most conserved component of lipopolysaccharide (LPS), with toll-like receptor 4 (TLR4) serving as the primary receptor **(Needham et al., 2013).** Despite this, there is significant diversity in LPS constructions, including variations inside lipid A. Because of this variability, the capability of various LPS architectures to provoke the host resistant reply varies **(Scott et al., 2017; Needham et al., 2013).**

LPS as neuroinflammatory agent:

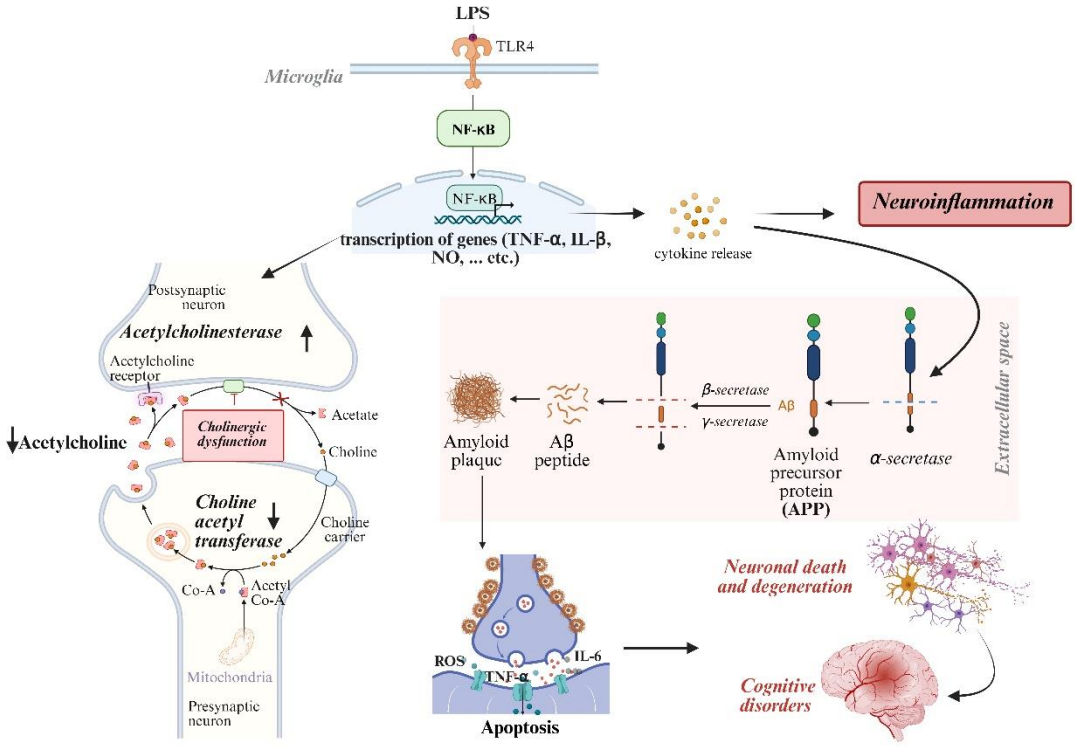

Figure 3. LPS as a neuroinflammatory agent.

LPS is frequently castoff in investigational in vitro and in vivo models of amyloidosis also neuroinflammation **(Whitton, 2007; Miklossy, 2008; Anaeigoudari et al., 2016).**

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Gram-negative bacteria's outer membrane contains LPS, a strong endotoxin that is incredibly resistant to being depleted by mammalian enzymes. Because of the chronic inflammation it produces, proinflammatory cytokines are produced **(Zhao et al., 2004; Walter et al., 2006)**. According to **Maitra et al. (2012),** these proinflammatory cytokines trigger reactions akin to those brought on by behavioral stress by stimulating the neuroimmune and neuroendocrine systems.

Memory loss and cognitive impairment can result from these cytokines' ability to start a chain reaction of harmful events in the nervous systems. Furthermore, it demonstrated that when administering LPS increases the manufacture of pro-inflammatory cytokines and over-activates microglia **(Choe et al., 2024).** This sets off a cable of proceedings that results in both neuronal cell demise and a loss of synaptic plasticity. The dose, route, duration, age, and species of the animals can all affect the consequences of administering LPS **(Catorce and Gevorkian, 2016; Badshah et al., 2016; Bahaidrah et al., 2022).**

When it is injected intraperitoneally (i.p.) once or repeatedly, it can cause neuroinflammation and neurodegenerative consequences in the mouse brain that can last for up to 10 months **(Bossù et al., 2016).** Various pro-inflammatory mediators are formed, and neuroinflammation and neurodegeneration begin when the nuclear factor NF-κB pathway is stimulated by a variety of signaling pathways **(Shathiswaran et al., 2018).**

Astrocytes and microglia are chief causes of pro-inflammatory cytokines. Cytokines have been demonstrated to be induced by both a single and recurrent systemic dose of LPS **(Miraz-Riose et al., 2013).** Additionally, by affecting hippocampus neuronal activities like cognitive abilities and working memory consolidation, the overproduction of pro-inflammatory mediators interferes with important learning and memory processes **(Dinel et al., 2016).**

When lipopolysaccharide (LPS) is administered, neuroinflammatory cytokines and chemokines are released, which increase β-secretase (BACE) activity and promote amyloid formation in the brain **(Lee et al., 2008).** Besides neuroinflammation, systemic LPS injection has been linked to elevated intracellular amyloid β buildup and processing of amyloid precursor protein (APP), both of which impair memory **(Thapa et al., 2016).**

Studies have demonstrated that LPS administration, which boosts Aβ synthesis and disrupts synaptic activity, results in impaired spatial learning performance **(Zhang et al., 2015).**

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Additionally, research using transgenic animal models has shown that overexpression of TNF-α and IL-6 leads to cognitive impairment **(Zheng et al., 2016).**

Hypersomnia, fever, and decreased food intake, are among the generalized behavioral possessions known as "sickness behaviors" that are brought on by LPS **(Zakaria et al., 2017).**

LPS's central nervous system (CNS) mechanism of action:

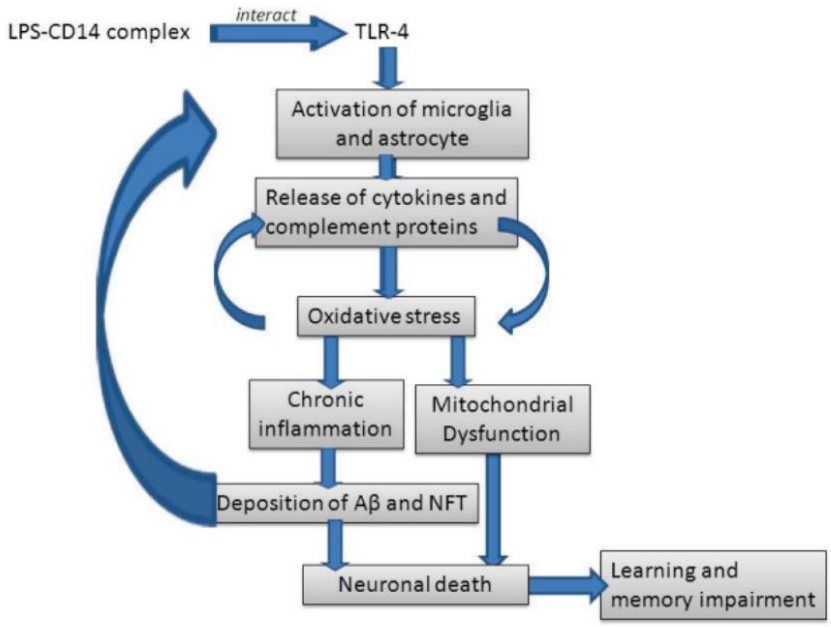

Figure 4. Mechanism of LPS action in CNS (Zakarai et al., 2017)

The LPS-CD14 complex is created when lipopolysaccharide (LPS) attaches to CD14 on microglial membranes. This complex then cooperates through the toll-like receptor (TLR)-4 **(Lehnardt et al., 2003; Hansen et al., 2000).** Microglia are activated by this interaction, which starts signal transduction cascades that cause proinflammatory cytokines to be rapidly synthesized and released **(Sun et al., 2015).** Furthermore, complement system proteins including C3 and C3a receptors **(Rivest, 2009)**, chemokines like CCL2 and anti-inflammatory cytokines **(Welser-Alves and Milner, 2013)** and IL-10 **(Zakaria et al., 2017**) are created. It has been shown that three days of LPS injection significantly elevated the countenance levels of cytokines in the hippocampus related to controls **(Daulatzai, 2016; Radford-Smith et al., 2023).**

Proinflammatory cytokines are important immune response regulators. Their ongoing presence worsens dyshomeostasis in chronic inflammation **(Ghosh et al., 2015; Zhang et al., 2000).**

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Long-lasting irritation is characterized via enduring stimulation of microglia, which increases oxidative and nitrosative stress and maintains the announcement of inflammatory mediators. According to **Tansey et al. (2007),** this prolongs the inflammatory cycle, which is detrimental in a number of neurodegenerative illnesses **(Block and Hong, 2005; Wang et al., 2023).**

NO, ROS, mitochondrial dysfunction, and proinflammatory cytokines are all elevated in overreactions to inflammation. Redox-glutathione depletion, mitochondrial respiratory failure, and damage to the systemic vascular endothelium can all result in decreased ATP and O2 consumption. Accordingly, oxidative stress and inflammation are allied to the etiology of AD (**Lowes et al., 2013).**

It has been demonstrated that inflammatory cytokines enhance the production of amyloid β **(Zakaria et al., 2017).** β-secretase mRNA, protein, and enzymatic activity are transcriptionally increased by cytokines **(Sastre et al., 2003).** Aβ synthesis is greatly decreased or stopped in the absence of β-secretase, a crucial rate-limiting enzyme that starts Aβ generation (**Vassar, 2001; Walter et al., 2001).**

According to research, LPS-induced inflammation increases the pathophysiology of AD by changing the way that Aβ is transported across the blood-brain barrier (BBB) and declining the amount of Aβ that is cleared centrally **(Erickson et al., 2012).** BBB alterations cause an increase in Aβ influx of the brain and a decrease in its outflow **(Jaeger et al., 2009).** Aβ countenance levels in the hippocampus are markedly higher than in controls following LPS injection **(Daulatzai, 2016; Brown et al., 2024).**

Inflammation hypothesis:

The effect of lipopolysaccharide (LPS) on neuroinflammation in Alzheimer's disease (AD) will be examined in this review. According to recent research, AD is also characterized by aberrant gliosis and neuroinflammation. The inflammatory theory has been validated by genetic and transcriptome studies, which have identified pathways linked to microglia as important risk factors for AD and its pathophysiology. **(Song et al., 2017).**

For instance, microglia and related proteins, may have an impact on synaptic damage in the initial phases of AD **(Hong et al., 2016).** Lasting potentiation can be greatly impacted by the

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progressions of activity-dependent and lasting synaptic elasticity, which are essential to learning and memory.

Consequently, aberrant microglia and astrocytes encircle amyloid plaques and release a variety of proinflammatory cytokines. These occurrences aid in the development of AD. Nonsteroidal anti-inflammatory medicines (NSAIDs) haven't worked well in therapeutic settings, though. This could be because innate immunity and AD pathogenesis have a complicated interaction in which immune responses can either be helpful or harmful **(Baruch et al., 2016).**

Better treatment strategies and diagnostic techniques for Alzheimer's disease (AD) are being made possible by recent studies understanding the processes of microglial disturbance in synaptic pruning, neurogenesis, and plasticity regulation. Restoring homeostasis and comprehending the aberrant functions of microglia may provide novel approaches to treating AD. Newfangled biomarkers that represent the actions of particular microglia are desperately desired, nevertheless, because of the assorted and intricate parts that microglia play in both health and sickness **(Jevtic et al., 2017).**

A numeral of neurodegenerative illnesses, including AD are linked to neuroinflammation, which is defined by glial cell instigation and the construction of important inflammatory mediators **(Amor et al., 2010).** Neurodegenerative diseases, including AD, progress as a result of excessive neuroinflammation. Prominent astrogliosis, raised stages of pro-inflammatory mediators and cytokines, and microglial instigation are all indicators of neuroinflammation in the brains of AD patients **(Ramesh et al., 2013).**

Inflammation is regulated by numerous mediators, with NF-κB being the essential manager and the most extensively studied target due to its critical role **(Lin and Karin, 2007; Lin et al., 2013).** The activation of NF-κB, especially its constitutive activation in chronic inflammatory patients, has been associated with numerous human diseases, together with Alzheimer's disease, and this is considered an autoimmune/inflammatory condition **(Gupta et al., 2010b; Yang et al., 2022).**

Notwithstanding these discoveries, more investigate is still needed to discover the fundamental causes of Alzheimer's disease in addition the processes influencing its progression, some of which have been found to be contributing factors **(Mahdi et al., 2019).**

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Members of the NF-κB Family and Disease Management:

Ledoux and Perkins, (2014) stated that NF-κB has an impact on nearly entirely cell categories in the body and is necessary for inflammation, immunological replies, cell cycle regulation, and cell survival. This transcription factor is made up of the five members of the Rel family in mammals. The Rel homology domain (RHD), a similar amino acid sequence that these members share, is composed of about 300 amino acids **(Chen and Greene, 2004).**

Subunits of triggered NF-κB come together to procedure homo- or hetero-dimerized transcription factor complexes that have the capacity to bind DNA and transactivate. The most well-researched type of NF-κB is a heterodimer made up of the p50 and p65 subunits, which is a potent transcriptional activator **(Shih et al., 2015).**

NF-κB can be activated by a variety of stimuli, including cytokines, carcinogens, tumor promoters, ultraviolet (UV) radiation, viruses, bacterial toxins such as lipopolysaccharide (LPS), oxidative stressors such free radicals and cigarette smoke, and other mitogens **(Gupta et al., 2010 a, b).**

Numerous autoimmune or inflammatory diseases have been allied to the instigation of NF-κB, particularly when constitutively stimulated in patients with long-lasting irritation **(Gupta et al., 2010b).** Supplementary, it is known that a number of natural or artificial materials, including immunosuppressive medications, interferons, endocrine hormones, phytochemicals, corticosteroids, and Th2 cytokines, inhibit signaling pathways and overwhelm NF-κB instigation **(Ahn and Aggarwal, 2005).** As a result, NF-κB regulation and dysregulation are essential for managing disease.

The NF-κB Family Affiliates in the Brain Position:

NF-κB transcription factors are abundantly expressed in the brain. The brain has been shown to express NF-κB at higher basal levels than peripheral tissues **(Shih et al., 2015).** The developing rat brain has all NF-κB complexes of heterodimer, and homodimer **(Bakalkin et al., 1993).** Research on the distribution of NF-κB has shown that neurons have high expression of the released p65 and p50 NF-κB subunits. Furthermore, p50/p65 heterodimers are found in the adult brain's cell nucleus and show constitutive activity **(Meffert and Baltimore, 2005).**

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Neuroinflammatory Mediators and NF-κB:

Among the numerous molecules and factors that control inflammation are adhesion molecules, vascular cell adhesion, endothelial leukocyte adhesion molecules, chemokines, cytokines, and proinflammatory transcription factors (NF-κB) **(Aggarwal, 2004).** The primary regulator of inflammation among these mediators is NF-κB. For instance, endothelin-1 can also cause proinflammatory cytokines and proinflammatory enzymes in the rat brain, and LPS can simulate a bacterial infection (**Lin et al., 2013**).

Extra 500 genes allied to inflammation-related responses have been found to be stimulated by NF-κB **(Gupta et al., 2010a, b).** Because of its crucial function, the NF-κB family is thought to be the furthermost expansively researched target in the inflammatory problem **(Chen and Greene, 2004; Lin and Karin, 2007).** Numerous neuro-inflammatory stimuli might momentarily activate NF-κB, leading to neuroinflammatory reactions **(Yakovleva et al., 2011).** According to **Niranjan (2013)**, NF-κB has a serious role in controlling the pathophysiology of diseases linked to neuroinflammation.

Impact of NF-κB on Pain-Related Inflammatory Responses:

In glia cells, NF-κB is highly inducible and has reduced basal activity, making it a significant contributor to inflammation in the brain. The function of glial NF-κB in pain research has received more attention. Certain high-threshold PNS neurons called nociceptors may produce pain signals as a detecting mechanism to stop additional damage **(Kaltschmidt and Kaltschmidt, 2009)**.

Both chronic inflammation (inflammatory pain) and nerve system damage (neuropathic pain) can produce pain signals in a clinic **(Nieder-berger et al., 2007).** Furthermore, after spinal cord injury, astroglia NF-κB suppression can improve functional recovery and reduce inflammation **(Brambilla et al., 2005).** All these consequences argument to the importance of NF-κB in the central nervous system for inflammatory pain.

Alzheimer's disease (AD):

Through the activation of astrocytes and microglia, neuroinflammation is one of the four main alterations in the brain that lead to AD. Inflammation is believed to be beneficial under normal

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conditions, but an overabundance of inflammation can be detrimental to the body, including the brain **(Calsolaro and Edison, 2016).**

We now know that the brains of people with Alzheimer's disease change in four important ways. First, it is supposed that amyloid peptide (Aβ)-based extra-neuronal plaques develop initially as a result of an disparity among Aβ synthesis and approval, which leads to accumulation it **(Raskin et al., 2015; Ricciarelli and Fedele, 2017).** Second, there are intraneuronal fibrils called paired helical filament neurofibrillary tangles, which are mostly made of hyperphosphorylated tau protein. Tau protein is necessary for microtubule stability; however, Alzheimer's disease causes hyperphosphorylation of tau protein, which destabilizes microtubules. This is brought on by an imbalance in the activity of kinases and phosphatases **(Raskin et al., 2015).** Thirdly, according to **Calsolaro and Edison (2016),** neuroinflammation is another significant symptom that is believed to occur before Aβ impairment. Indeed, it seems that astrocytes and microglia undergo a transformation, leading to an overabundance of inflammatory responses and augmented levels of pro-inflammatory cytokines **(Fakhoury, 2018).** Finally, AD patients also exhibit brain atrophy, which is brought on by structural dysfunction and cell death, exclusively in the neocortex and hippocampal regions **(Raskin et al., 2015; Sun and Alkon, 2019).**

There are two distinct phenotypes of microglial cells: the traditionally activated M1 and the alternatively activated M2. When Toll-like receptors or interferon gamma (IFNγ) activate the M1, pro-inflammatory cytokines are released in an attempt to eradicate possible incursive infections. **(Calsolaro and Edison, 2016).**

In contrast, the M2 phenotype is brought on by IL-4 and IL-13 and results in the generation of anti-inflammatory cytokines that support angiogenesis and tissue repair. Aβ aggregates seem to exacerbate the activation of the M1 phenotype, which in crack causes the production of excessive quantities of pro-inflammatory cytokines, endangering brain homeostasis. Moderate microglia activation may help remove Aβ and yield neuroprotective substances like glial cell-derived neurotrophic factor, BDNF, and NGF, but it is insufficient to offer protection **(Fakhoury, 2018).**

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Conversely, astrocytes show a role in synaptic remodeling, neurotransmitter transmission, oxidative stress management, ion homeostasis, and BBB permeability modulation**.** Furthermore, the removal of Aβ may possibly include astrocytes **(Fakhoury, 2018).**

Nonetheless, it has been discovered that the degree of AD is directly correlated with the astrogliosis around amyloid plaques, that is considered via elevated astrocyte numbers and changes in their molecular expression and architecture **(Minter et al., 2016).** Even though astrocytes are ideally neuroprotective, in self-destructive situations, they may release pro-inflammatory cytokines. Furthermore, interactions between astrocytes and microglia may alter the latter's activation state (activating the M1 phenotype), diminish their capability to phagocytose, and concurrently increase the release of pro-inflammatory cytokines **(Fakhoury, 2018).**

Emil Kraepelin initially mentioned Alzheimer's disease (AD) in 1908. Emil Kraepelin, a psychiatrist and neuropathologist who worked with Aloysius Alzheimer, was the first to chronicle the strange and progressive illness that left one of his patients disoriented and memory impaired. Alzheimer investigated the autopsy brain of his patient and found abnormal deposits, now called neurofibrillary tangles and senile plaques, along with a shrinkage in brain size **(Health et al., 2018).** It is believed that the main cause of Alzheimer's disease is the buildup of aberrant deposits of malfunctioning proteins in the brain.

The greatest predominant form of dementia, Alzheimer's disease (AD), is a debilitating, progressive neurological illness for which there is currently no known cure **(Alzheimer's Association, 2016).** It is categorized by a number of cognitive and neuropsychiatric symptoms that make it harder to do daily tasks, including memory damage, impaired spatial and temporal alignment, and neuropsychiatric problems**.** The decline of neurons in the cortex and hippocampus, the particular regions of the brain most in charge of cognitive functions, is the main cause of these detrimental effects **(Raskin et al., 2015).** Cognitive and functional abilities deteriorate because of brain changes brought on by the disease, such as reduced information transfer through synapses, which leads to neuron death **(Alzheimer's Association, 2016).**

There are two categories of ADS: the familial early-onset variety, which makes up 1-5% of all cases, and the most prevalent, sporadic late-onset variant. These conditions result in Alzheimer's disease, that manifests among the ages of 30 and 65 and is caused by a familial hereditary a etiology concerning alterations in the genes programming **(Chu, 2012).**

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Alzheimer's disease is supposed to start one or two decades before the first symptoms occur, despite the fact that the sporadic late-onset type of the disease has been seen in adults over 65 **(Duthey, 2013).**

In the initial years, there were no cyphers or signs of AD because the brain can adapt to the changes brought on by the illness. However, when the illness worsens, symptoms appear, and the brain becomes unable to undo the negative consequences. The main hereditary danger issue for this late-onset AD is the ApoE4 gene. Therefore, this late-onset disease may be influenced by various factors **(Qiu et al., 2013).**

According to **Minter et al. (2016),** all of the aforementioned detrimental impacts impair the functioning of microglia and astrocytes and interfere with the blood-brain barrier, resulting in neuroinflammation and neurodegeneration. Thus, there is no denying that neuroinflammation contributes to Alzheimer's disease, but further investigation is required to ascertain whether it causes the illness directly or as a consequence of it.

Conclusion:

LPS crossing the blood brain barrier and bind to toll like receptor on the surface of the microglia, this receptor recognizes the foreign molecules and initiates immune response. This complex after activation it translocate to the nucleus of microglia and activate NF-κB, transcription factor, which activate genes of inflammatory cytokines and release it to the brain environment which make proinflammatory state and damage neurons.

Also, these inflammatory cytokines activate α secretase which work on amyloid precursor protein producing amyloid beta which accumulates together and forming amyloid plaques between neurons causing Alzheimer’s disease.

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Conflict of interest statement

The author declares that they have no conflict of interests.

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Author's contributions

Ola Mohamed conducted the literature review and droughted the initial article. The other authors were responsible for the study's conceptualization, planning, and execution. All authors evaluated and approved the final version of the text.

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