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UNVEILING THE COMPLEX ROLE OF NF-KB IN ALZHEIMER'S DISEASE: INSIGHTS INTO BRAIN INFLAMMATION AND POTENTIAL THERAPEUTIC TARGETS

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and dementia. One of thae major pathologies underlying AD is chronic neuroinflammation mediated by microglia and astrocytes in the brain. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway is a key regulator of inflammation and has been implicated in the neuroinflammatory processes associated with AD. This review comprehensively summarizes current findings on the complex role of NF-κB signalling in AD pathogenesis. The canonical and non-canonical NF-κB activation pathways are described, along with evidence from human studies and animal models demonstrating increased NF-κB activity in AD brains. The deleterious effects of NF-κB-mediated neuroinflammation are discussed, including the upregulation of inflammatory cytokines, chemokines, and enzymes that exacerbate neuronal damage over time. Targeting the NF-κB pathway is proposed as a promising therapeutic approach to dampen neuroinflammation in AD. Preclinical studies utilizing genetic or pharmacological inhibition of NF-κB are reviewed, and key challenges in translating these findings to clinical applications are analyzed. Overall, this review unveils the multifaceted contributions of NF-κB signalling to AD neuropathology and highlights anti-neuroinflammatory NF-κB modulation as a potential avenue for future AD treatments. Further research is warranted to fully elucidate the complex interactions between NF-κB and AD pathogenesis.

Keywords: Alzheimer's disease; NF-κB; Microglia; neurodegeneration; neuro-inflammation.

Introduction

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Alzheimer's disease (AD) is a progressive neurological condition that affects physical and cognitive abilities as people age [1-2]. According to the World Alzheimer's Report 2015, approximately 46.85 million people worldwide suffer from Alzheimer's disease (AD) or another form of dementia, and this number is expected to double by 2030 and potentially triple by 2050 [3-4]. Every year, more than 7.7 million new cases of dementia are reported [5]. In the United States alone, over 4 million individuals suffer from Alzheimer's disease (AD), which is a devastating and fatal neurodegenerative disorder that leads to a decline in cognitive and emotional functions.

The hippocampus, entorhinal cortex, basal forebrain, amygdala, frontal cortex, and inferior parietal cortex are crucial regions in the brain responsible for learning and memory, but in AD patients, these regions suffer from degenerating neurons and synapses [6]. The pathological hallmarks of AD include the development of neurofibrillary tangles, which are filamentous intracellular aggregates of the microtubule-associated protein tau, and plaque-like aggregates of amyloid-beta (Aβ) [7-9]. These abnormal features lead to the death of cholinergic neurons, which results in the deposition of Aβ protein and the formation of neurofibrillary tangles, hyperphosphorylated tau protein production, gliosis, and neuronal loss [8-9]. Additionally, oxidative stress, excitotoxicity, neuro-inflammation, and neurotransmitter deficiencies are all associated with the accumulation of tau tangles and extracellular Aβ deposits [10-11]. The loss of cholinergic neurons in cortical and hippocampal areas has also been linked to AD [13-14], and the way serotonergic, glutamatergic, dopaminergic, and adrenergic neurons operate is affected as well [15-16].

Microglia cells have been implicated in AD pathogenesis since the mid-1980s, and both amyloid plaques and neurofibrillary tangles have been shown to activate microglia and astrocyte cells [17]. These activated cells release pro-inflammatory cytokines, chemokines, interleukins, prostaglandins, leukotrienes, and thromboxane’s, leading to neuro-inflammatory responses that contribute to disease progression [18-20]. Aβ-sites interaction with astrocytes increases pro-inflammatory mediator secretion, further exacerbating neuro-inflammation [20]. Amyloid beta also increases nitric oxide production, causing inflammation and neuronal death [21].

When microglia are exposed to Amyloid beta, they produce inflammatory cytokines such as TNF-alpha and IL-1beta [22]. Amyloid stimulates microglia through a calcium influx-based mechanism, as per research by Landreth and colleagues [23]. Microglia expressing PS1 showed abnormal calcium homeostasis and increased inflammatory cytokine response when challenged with bacterial lipopolysaccharide (LPS) [24]. The sensitivity to LPS was higher in microglia from PS1 mutant mice than wild-type mice, indicating a negative effect of PS1 mutations and Amyloid beta on microglial cells under pro-inflammatory conditions [24-25]. These findings suggest that calcium responses may influence the neurodegenerative process in AD patients with PS1 mutations [25]. In the current review, we have discussed microglia and neuroinflammatory events and their association with Aβ and NFT pathology and cognitive decline in sporadic Alzheimer’s disease.

Role of NF-κB signalling in AD

Neuroinflammation occurs when NF-κB initiates the production of cytokines, chemokines, NO, and COX-2. This activation of microglia results in their proliferation, migration, and initiation of phagocytosis. T cells also contribute to the activation of this cascade, which generates pro-inflammatory cytokines and hazardous chemicals causing neurotoxicity. Ultimately, this leads to neuronal dysfunction and death. Neuroinflammation refers to the inflammation that occurs within the brain and spinal cord. This reaction involves the release of cytokines, chemokines, and ROS in response to astrocytes and microglia. Microglia, which serve as the primary immune surveillance in the CNS, also produce cytokines and chemokines, similar to macrophages. These neuroinflammation responses are characterized by various pro-inflammatory cytokines, including interleukin-1, interleukin-6, TNF-, different chemokines (CXCL-1, CCL2, CCL5), nitrous oxide, PGs, and ROS. Inflammation plays a significant role in several metabolic diseases, including diabetes, atherosclerosis, and multiple sclerosis, as well as in neurodegenerative illnesses such as Alzheimer's disease (AD) [28].

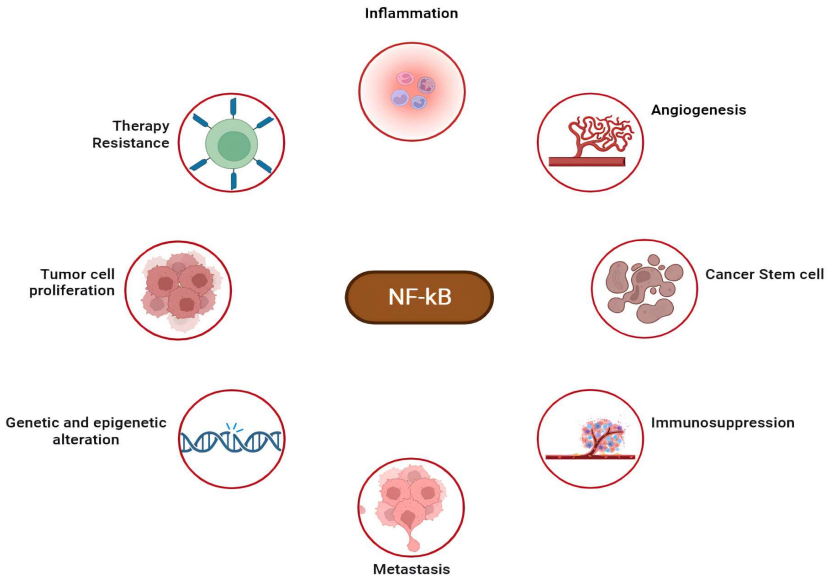

Figure 1: *Roles of NF-κB. Nuclear factor-κB (NF-κB) directly and indirectly controls inflammation, cancer cell proliferation and survival, angiogenesis and metastasis, as well as genetic and epigenetic alterations, cancer stem cell formation, cellular metabolism and therapy resistance. NF-κB activation also induces immunosuppression via several mechanisms.*

The synthesis of NF-kB protein is strictly regulated in both the cytoplasm and the nucleus6. I-B family proteins, comprising I-B, I-B, and I-B (also referred to as NF-κB I, NF-kBI, and NFkB - BI, respectively), directly interact with NF-kB complexes to keep them inactive in the cytoplasm under normal physiological conditions. The NF-kB complex's nuclear localization domains are hidden by I-B proteins, which keeps the transcription complex in the cytoplasm. Toll-like receptors (TLRs), as well as cytokine receptors such as interleukin-1 receptors (IL-1Rs), TNF receptors

(TNFRs), and other TNFR-like receptors, can quickly activate the NF-kB complex in response to a range of pro-inflammatory stimuli.

How to activate the neuronal NF-kb pathway

Activators

Intracellular Ca^{2+}, glutamate, NMDA, Aβ amyloid Mutation, bacterial infections, mitochondrial malfunction, saturated fat and traumatic brain injury. Elevated levels of amyloid beta protein in the brain have been observed in both animal models and AD patients, accompanied by microglia activation and microgliosis. Microglia activation is detected early in the disease course. The inflammasome, a cytosolic protein complex that

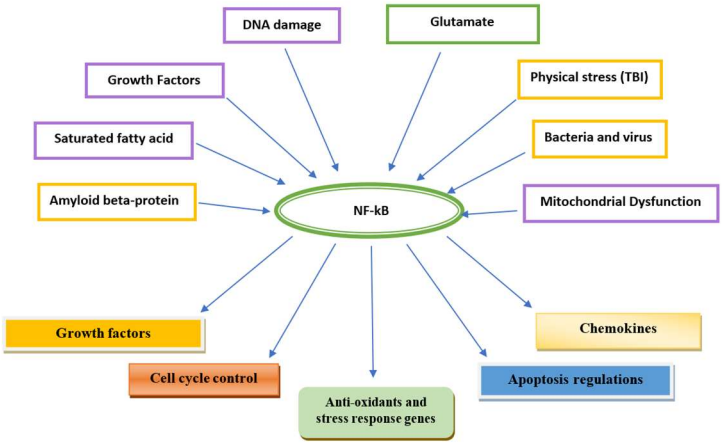

***Figure 1**: Activations of NF-κB transcription factor*

activates caspase-1 to promote IL-1 production and release, has been shown by Halle et al. to be activated by internalized AD, resulting in increased production of other potentially inflammatory and neurotoxic mediators. Studies have also reported the presence of pro-inflammatory cytokines like IL-6 and TNF in greater quantities in the brains of AD patients. In addition to its direct neurotoxic effects, microglia activation also promotes amyloid beta buildup.[28]

Microglial NF-κB signalling activation by Saturated fatty acid

The activation of microglial NF-κB signalling by saturated fatty acids (SFA) was observed in both BV-2 cells and primary microglial cells. Our research showed that SFA exposure led to microglial activation, which was characterized by changes in cell shape indicative of a reactive phenotype, and an increase in the production of reactive oxygen species (ROS), nitric oxide (NO), and proinflammatory cytokines like TNF-a, IL-1b, and IL-6. This, in turn, caused the death of nearby neurons. We also found that PA administration, similar to LPS, induced an expression of IL-1b and iNOS. In addition, PA treatment activated NF-κB. Notably, blocking NF-κB activation using the inhibitor PDTC prevented the expression of iNOS, TNF-a, IL-1b, and IL-6 mRNA, as well as the production of TNF-a, IL-1b, and NO, except for IL-6. Another important observation was the

inhibition of PA-induced NF-κB activation and the generation of pro-inflammatory mediators in cells treated with antiTLR4 Ab. These findings suggest that SFA can activate microglia and stimulate the TLR4-NF-κB pathway, causing the release of pro-inflammatory mediators that may contribute to the death of neurons. [29]

Traumatic brain injury (TBI) induces the activation of microglial NF-κB signalling

Activation of NF-κB is a consequence of traumatic brain injury, which can trigger self-perpetuating inflammatory responses in the brain (30, 31). In Drosophila flies affected by TBI, symptoms such as transient incapacitation, ataxia, activation of the innate immune system, neurodegeneration, and death have been observed, resembling human TBI (32, 33). In rat models, NF-κB has been found to be acutely upregulated and persistently overexpressed in the brain regions most frequently associated with post-injury atrophy (34, 35).

The activation of microglial NF-κB signalling by glutamate

The overactivation of glutamate receptors in neurons can cause damage due to increased glutamate concentrations, which is a symptom of excitotoxicity. This excessive release of glutamate can activate NF-κB signalling, leading to the production of numerous proinflammatory proteins. Increased glutamate results in Ca^{2+} influx through the NMDA receptors, which activates various proteases, nitric oxide, and reactive oxygen species that damage cells. The NMDA-mediated enhanced Ca^{2+} influx stimulates NF-κB, which is translocated into the nucleus and worsens the inflammatory feedback loop [36, 37].

Activation of microglial NF-κB signalling by microbial infection

Some viruses such as HIV-1, human T-lymphotropic virus 1 (HTLV-1), hepatitis B and C viruses, rotaviruses, influenza viruses, and respiratory syncytial viruses (RSVs) have developed mechanisms to actively stimulate the NF-κB activation to increase viral replication and prevent virus-induced apoptosis. As a result, activated NF-κB becomes essential for viral gene expression, replication, and propagation. All these viral genomes have important gene promoters with NF-κB-binding sites, and the infection's prolonged activation of both the traditional and alternative pathways of the NF-κB pathway cause excessive inflammation through the production of NF-κB-regulated pro-inflammatory cytokines and chemokines. The host superoxide-producing enzyme NOX2-containing NADPH oxidase activates the traditional NF-κB pathway in airway epithelial cells by phosphorylating I-B and RELA via RIG-I (DDX58), TRAF6, and IKK, while the kinases NIK and IKK activate the alternative NF-κB pathway, causing nuclear translocation of p52-RELB. [38-43]

Alzheimer's disease and the microglial NF-κB pathway

The immune cells responsible for the CNS are called microglia (44). The functional properties of these cells have attracted growing attention since it was discovered that microglia are the primary

source of brain immune mediators. The activation of microglia has been linked to the destruction of neurons in conditions like trauma (45) and Alzheimer's disease. These cells can release cytotoxic substances, such as proteases, excitatory amino acids, arachidonic acid derivatives, cytokines, and free oxygen intermediates (46).

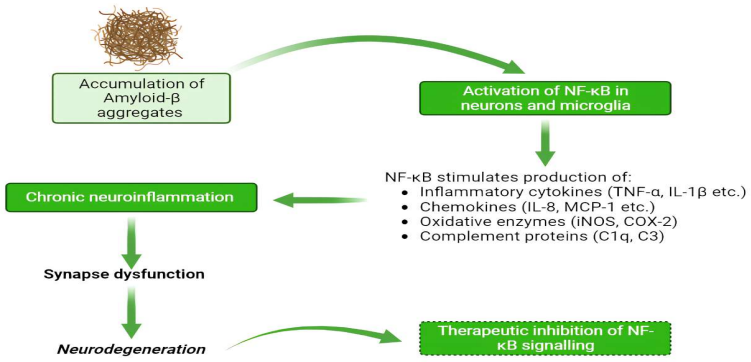

Figure 3: Amyloid-beta aggregates trigger activation of NF-κB signaling in neurons and microglia, leading to neuroinflammatory responses that mediate synapse dysfunction, neurodegeneration, and cognitive decline. Therapeutic inhibition of NF-κB may block this deleterious cycle.

Activation of NF-κB can be initiated by various factors. Additionally, it is possible that autocrine and paracrine activation loops are responsible for elevated constitutive NF-κB activity. It is also hypothesized that NF-κB activation signalling is linked to synaptic events that trigger transcription. Research suggests that inducible NF-κB activity in glial or endothelial cells is essential for neuro-inflammation and is associated with secondary neuronal injury. Inflammatory processes, which are specifically regulated by increased NF-κB in glial cells, worsen several diseases, including Alzheimer's disease.

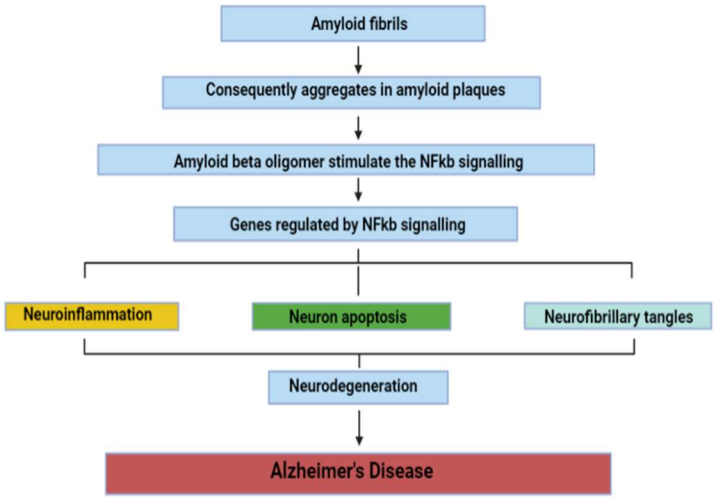

Figure 4: Link between Alzheimer's disease and NF-κB signalling.

Glial cells-mediated inflammation can exacerbate the hallmark histological features needed for Alzheimer's disease (AD) diagnosis, such as amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFT) in neurons [47]. This, in turn, promotes neuronal instability and loss [48], which creates a vicious cycle of neurodegeneration, primarily driven by NF-κB [49]. Nonetheless, the activation of NF-κB can have a dual function in either neuroprotection or neurodegeneration, depending on the cell type and/or the mix of NF-κB subunits [50]. Previous studies have shown that pro-apoptotic genes are produced that trigger neuronal death by activating p65/p50 dimers, whereas c-Rel-containing dimers control the production of genes that prevent apoptosis and promote neuronal survival. Interestingly, p65/p50 heterodimers or c-Rel can be selectively activated depending on the type of stimulus received, such as IL-1, Nerve Growth Factor (NGF), Aβ peptide, or glutamate [51][52].

NF-κB is essential in the pathophysiology of AD, as it controls several molecules that contribute to the disease's morbidity. In the following section, we will summarize the common factors involved in the pathophysiology of hyperactive NF-κB signalling in AD.

Glutamate and NF-κB in AD

NF-κB-induced glutamate excitotoxicity triggered by amyloid oligomers is a critical component of the Alzheimer's disease (AD) neurodegenerative cascade.

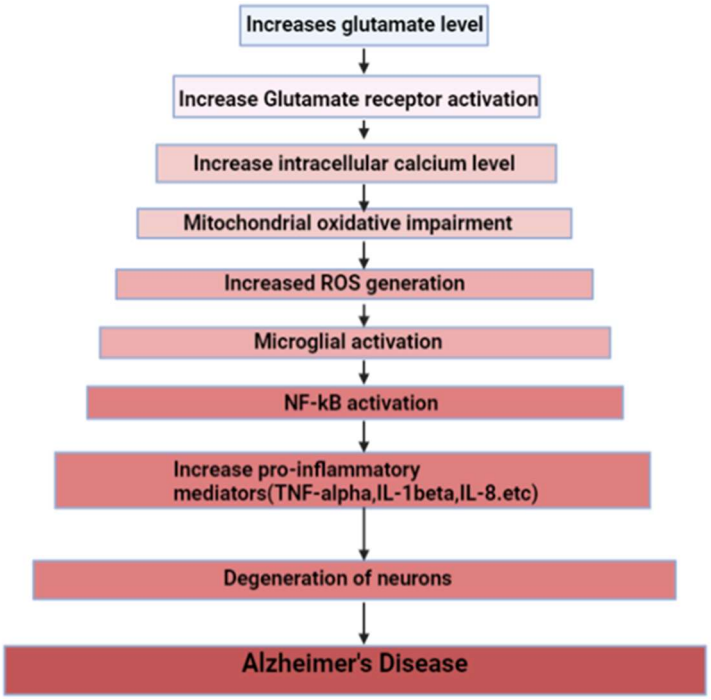

Figure 5: Link between Glutamatergic pathway and NF-κB signalling

Aβ peptides have been found to promote glutamate receptor activation and a concomitant increase in intracellular calcium levels in human cerebral cortical neurons. Long-term increases in intracellular calcium levels lead to microtubule instability, increased tau phosphorylation by calcium-dependent kinases, reduced mitochondrial oxidative capacity, and ultimately increased reactive oxygen species (ROS) production [53][54]. A study by Lim et al. validated hippocampal astrocytes from AD patients with elevated levels of calcium and metabotropic glutamate receptor 5 (mGluR5) around Aβ plaques. According to their findings, Aβ42 raises cytosolic calcium levels by triggering calcineurin (CaN), which allows the transcription of mGluR5 under the control of the NF-κB pathway. It was also demonstrated that the dephosphorylation of B-cell lymphoma 10 (Bcl10) by CaN might have contributed to the activation of NF-κB by CaN [55]. Bcl10 ubiquitinates IKK-I, which activates the NF-κB pathway [56]. Similarly, hippocampal astrocytes stained with mGluR5 co-localize with the accumulated nuclear p65 subunit of NF-κB, supporting the notion that NF-κB and glutamate work together to promote AD-like pathology [55].

NF-κB and *β*-Secretase in AD

Patients diagnosed with AD typically have high levels of NF-κB in their cerebral cortex, which is linked to elevated levels of APP cleaving enzyme-1 (BACE1). According to a previous

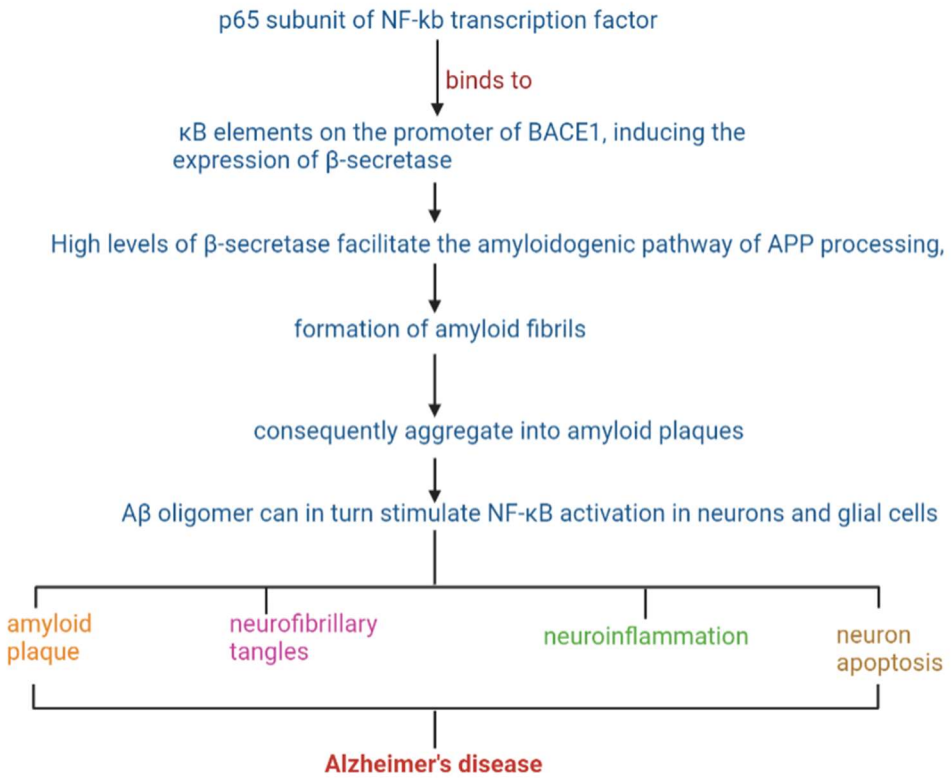

Figure 6: Link between Secretase and NF-κB signalling.

study, the NF-κB p65 B subunit binds to the B elements on BACE1's promoter and activates the expression of β-secretase [57]. The high levels of β-secretase facilitate the amyloidogenic route of APP processing, which leads to the formation of amyloid fibrils and their subsequent aggregation into amyloid plaques [58]. Furthermore, Aβ oligomers themselves can induce NF-κB activation in glial and neuronal cells [59]. In primary and N2TN neurons, the Aβ 40 peptide was shown to strongly activate the p65/p50 dimers of NF-κB and increase the production of pro-apoptotic genes. Bax, p63, DcR2, and TANK (TRAF family member-associated NF-κB activator) are some of the genes that are induced after Aβ-40 stimulation, and they all contain B regulatory elements in their promoter regions. Additionally, Aβ 40 accelerated the formation of Aβ 42 aggregates, further accelerating the neuropathological cascade of AD [60]. Similarly, Aβ peptide has been demonstrated to cause toxicity in primary neurons and cell lines by increasing peroxide generation, a source of oxidative stress. Reactive oxygen species (ROS) are known to activate NF-κB subunits in certain cases, and our research implies an indirect relationship between Aβ peptide-mediated toxicity and NF-κB activation, which is also associated with high levels of NF-κB signalling [61].

How the NF-κB signalling pathway in the microglia can be turned off to treat Alzheimer's disease

Microglia become activated and release inflammatory cytokines such as interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha) in response to AD [62]. Landreth et al. [63] found that amyloid stimulates microglia through a calcium influx-based mechanism. Current drugs approved by the US Food and Drug Administration (FDA) for the treatment of AD provide symptomatic relief, but do not significantly address the underlying causes or halt the disease's progression [64]. Research has focused on targeting the mechanisms of AD, particularly the A cascade, to prevent toxic amyloid formation [65]. An effective strategy to stop AD progression and neurodegeneration is to prevent tau pathology [66]. Furthermore, continuous use of non-steroidal anti-inflammatory drugs (NSAIDs) is linked to a significant reduction in the risk of developing AD, depending on when treatment is initiated [67].

Calcium and glutamate receptor blocker

Patients with AD who participated in clinical studies of the L-type voltage-dependent calcium channel blocker nimodipine showed small improvements in several of their symptoms [68]. Patients with severe dementia have reportedly benefited from the use of memantine, an uncompetitive NMDA receptor antagonist [69]. These findings point to a potential advantage of calcium influx-suppressing medications. However, these medications might potentially impair the way that calcium influx-dependent neurons normally function.

NSAIDs: Non-steroidal anti-inflammatory medications

During patient clinical studies, the majority of NSAIDs were ineffective at treating AD (70). However, early indomethacin therapy for AD patients (71) and a post-naproxen analysis from the ADAPT (Alzheimer's disease anti-inflammatory prevention trial) research group showed

promising results in preventing the development of AD (72). Aspirin, on the other hand, proved ineffective in treating AD patients in the AD 2000 experiment and significantly raised the risk of suffering life-threatening bleeding.

β-Secretase inhibitors and modulators: The amyloidogenic APP pathway is processed at its first stages by the secretase enzymatic complex. LY2886721 (NCT01807026 and NCT01561430), MK-8931 (NCT01739348), and E2609 (NCT01600859) all successfully lower Aβ production in the cerebrospinal fluid (CSF) in people by about 80–90%. There are currently no β-secretase inhibitors on the market to treat AD (73).

α-Secretase inhibitors and modulators:

Aβ peptides are produced by the α-secretase complex, which takes part in the last phase of amyloid formation. A α-secretase inhibitor semagacestat (LY450139) reduced Aβ levels in human blood and cerebrospinal fluid (CSF). The NCT00762411, NCT01035138, and NCT00762411 clinical trials were unsuccessful and showed no efficacy against AD. In therapeutic trials with AD patients, another -secretase inhibitor called Avagacestat was equally ineffective (NCT00810147, NCT00890890, NCT00810147, NCT01079819) (74). Active vaccination for the pathophysiology of AD In mild-to-moderate AD patients, an active immunisation study was conducted using the AN-1792 Alzheimer vaccine (NCT00021723), which is a synthetic full-length Aβ-42 peptide combined with QS-21 adjuvant. However, it caused severe meningoencephalitis in about 6% of patients, so it was abandoned in Phase II trials (75). The immunogenic Aβ-6 peptide in CAD106 functions as a B-cell epitope while preventing a T-cell response (76). CAD106 is currently undergoing Phase II/III clinical trials in cognitively normal individuals carrying two ApoE4 genes (NCT01097096 and NCT02565511).

Novel treatment strategies:

Anti-Amyloid monoclonal antibody: Monoclonal antibodies designed to target amyloid, known as anti-amyloid MABs, are reshaping the landscape of Alzheimer's disease (AD) treatment. Notably, drugs like Aducanumab and Lecanumab are leading the charge. These medications are engineered to bind specifically to amyloid aggregates, and their early-phase trials have yielded positive outcomes. What sets them apart is their ability to target amyloid aggregates in both oligomeric and fibrillar states, a departure from conventional approaches that focus solely on amyloid monomers. These drugs, such as Aducanumab and Lecanumab, offer the potential to rejuvenate neurological function in AD patients by diminishing Aβ plaques and restoring neuronal calcium permeability [77]. The impact of these innovative therapies cannot be overstated. They provide new hope for patients who were previously confronted with the inexorable progression of AD. Moreover, these treatments represent a pioneering approach that paves the way for the development of other disease-modifying treatments and combination therapies. As we embrace these transformative therapies, it's crucial to acknowledge that they bring forth fresh challenges and opportunities for the various stakeholders in AD care. To accommodate these groundbreaking

treatments, we need to foster global innovations in social and medical care. The advent of anti-amyloid MABs is a remarkable milestone, marking the dawn of a new era in addressing the formidable challenges posed by AD—a step forward in safeguarding our most invaluable global asset: the human brain [78].

Conclusion

The development of Alzheimer's disease (AD) involves multiple factors, with inflammation being a prominent one according to several studies. A chronic inflammatory state arises from the imbalance between proinflammatory and anti-inflammatory cytokines, leading to delirium and cognitive decline. This research examines the roles of peripheral blood cells and microglia in AD pathogenesis and potential treatments for the disease. Specifically, the study reveals that microglia can be activated by factors such as SFA Amyloid beta protein, Saturated fatty acid, Traumatic Brain Injury, and microbial infection, triggering the NF-κB pathway and the release of pro-inflammatory mediators that may cause neuronal damage. One potential therapeutic approach is to inhibit NF-κB signalling, which could be achieved by blocking calcium channels or glutamate receptors, inhibiting alpha and beta secretase, and novel anti-amyloid monoclonal antibody among other strategies.

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