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Effectiveness of Ways to Treat Alzheimer's Via Studying Ways to Treat Inflammatory Processes in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common type of dementia and a neurodegenerative disorder. Histopathologically, two significant hallmarks, intracellular neurofibrillary tangles (NFTs) and extracellular neuritic plaques (NPs) enclosed by initiated astrocytes and microglia, define the disease. NFTs are made up of paired helical filaments of hyperphosphorylated fragment tau protein. The amyloid-peptide (**Aβ**), a small fragment of 50–52 amino acids with a molecular weight of 5 kD, is the primary aspect of the NP. It has been suggested that amyloid materials and microglia activation can promote the neurodegenerative process seen in Alzheimer's disease patients. However, the role of inflammation in Alzheimer's disease is debatable. In the early stages of the disease, inflammation may play a beneficial role in pathology, as activated microglia and astrocytes are thought to be involved in **Aβ** clearance.Nonetheless, chronic microglia signaling has been linked to increases in **Aβ** and potentially tau phosphorylation. Complement molecules, pro-inflammatory cytokines, acute inflammatory reactants, and other inflammatory mediators are upregulated in AD brains, possibly contributing to the neurodegenerative process. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown in clinical studies and animal models to reduce the risk of getting AD and reduce A accumulation. Eventually, more study is needed to find whether anti-inflammatory strategies can slow the neurodegenerative method which impacts such patients.

Keywords: neuro degeneration, neuro inflammation, anti-inflammatory strategies, astrocyte, pro-inflammatory cytokine, amyloid-β, Alzheimer disease, microglia, pro-inflammatory cytokine, anti-inflammatory approach.

INTRODUCTION: Alzheimer's disease (AD) seems to be the standard form of dementia in aged persons. Alzheimer's disease (AD) focuses on a specific progressive decline of cognitive and memory functions. The existence of neuritic plaques (NPs) and neuro fibrillary tangles on histopathology distinguishes it (NFTs). The causes of Alzheimer's disease can be characterized as familial or sporadic. The prevalence of domestic cases is low (6–12%) but also is linked to mutants in three different genes: presenilin-1 (PS1), presenilin-2 (PS2), and presenilin-3 (PS3). 2 (PS2), as well as amyloid precursor protein (APP-α) (Levy-Lahad et al., 1995; Goate et al., 1991; Chartier-Harlin et al., 1991; Murrell et al., 1991; Sisodia et al., 1999), Duff et al., 1996. Although the aetiology of sporadic Alzheimer's disease is multifactorial, age is the most critical risk

factor. . even though there are various environmental and genetic reasons, all patients share standard clinical behavior and create exactly equal brain lesions: NFTs composed of Tau (Ţ) protein and NPs composed of amyloid- (**Aβ**) peptides. These changes are indeed the outcome of post-translational adjustments and involve numerous genes, making AD a complicated multiple genetic neuro degenerative disorder. Aside from the multi-genic complexity of Alzheimer's disease, researchers now know that **Aβ** helps promote an inflammatory[1,2,3,4,5,6,7,8,9,10,11,12,13,14, 15] reaction facilitated by microglia and astrocytes, turn activates signal transduction pathways that may ultimately led to neuro degeneration. It is currently unclear regardless of whether brain inflammation in Alzheimer's patients is a primary or secondary symptom of the disease. Even though it once did think that the central nervous system (CNS) had been innate immunity, it is now well understood that some inflammatory process occurs typically in response to injury, disease, or Infection. The resident CNS cells that produce inflammatory mediators, including such pro-inflammatory cytokines, prostaglandins (PGs),[16,17,18,19,20,21,22,23] free radicals, complement factors, and adhesion molecules but instead chemokines, which might also acquire peripheral immune cells. One such review describes the molecular and cellular intermediaries involved in inflammatory reaction conditions with Alzheimer's disease, and several recent therapeutic approaches.

IN THE NEURO-INFLAMMATORY PROCESS, NPS AND Aβ:

NPS are extracellular reserves that comprise a highly insoluble fibrillar **Aβ** core created by 40–45 amino acid fragments enveloped by dystrophic neuritis, astrocytes, reactive and microglia, produced by devolving based on the biological (Iversen et al., 2000). **Aβ** is usually derived from **Aβ** -APP-α via beta-secretase and the multi protein gamma-secretase complex (Kang et al., 1999). An accumulation in the brain is among the main inflammatory conditions in Alzheimer's patients. The creation of these reserves triggers a cascade of cell functions that can elicit an [24-30]immune reaction wherein native cells, including such microglial can participate. **Aβ** accumulation in the parenchyma, as well as blood vessels, causes microglial flow of migrants. It promotes acute inflammatory reactions against the aggregates, likely to induce pro-inflammatory cytokines (TNF, IL-1, and IL-6), PGs (PGE2), reactive oxygen species (ROS), and the nitric oxide production (NO), which may eventually promote neuronal death (Figure 1). (Kitazawa et al., 2005; Akiyama et al., 2001).

MEDIATORS OF CELLULAR TRANSMISSION

MICROGLIA

Microglia are resident brain cells that develop from monocyte precursor cells all through embryogenesis that can provide the initial reaction to any CNS harm. Although Nissl reported such cells over a century ago, a mark was the one who definitively identified and characterized those (2013). The presence of activated microglia around NPS suggested that microglia play a role in the **Aβ** accumulation seen in Alzheimer's disease patients (Glenner et al., 1985); this hypothesis was supported by studies (Dickson et al., 1989; Rozemuller et al., 1987). Microglia are ordinarily inactivated; morphologically, such cells have such a small soma to branching processes. Once initiated by pathogens or injury, such cells undergo visible morphological alterations such as lowered morphogenesis and[31-41]

soma growth, amoeboid formation, and the expression of a wide variety of individual cellular surface markers (Town et al., 2006). NPS in the brains of Alzheimer's disease patients activates the inflammation mediated by microglia, resulting in pro-inflammatory cytokine secretion, which might also directly cause neuronal injury.In vitro cell cultures of microglia can phagocyte the amyloid peptide. Even so, ultra - structural assessment of tissues from Alzheimer's disease patients revealed no amyloid fibrils in the lysosomal containers of local microglia cells (Frackowiak et al., 1993). While microglia can phagocyte **Aβ** in vitro, their phagocytosis capacity is low. The unusual existence of macrophages trying to infiltrate from the periphery, which also started showing amyloid fibers in their endosomal compartments,[41-51] was an important observation (Akiyama et al., 1997; Wisniewski et al., 1992). We currently know that two types of phagocytic cells within the CNS can initiate the innate immune response: microglia and peripheral macrophages (Gate et al., 2011; Rezai-Zadeh et al., 2010). These macrophages are recruited into the CNS by specific cytokines and chemokines released during inflammation.

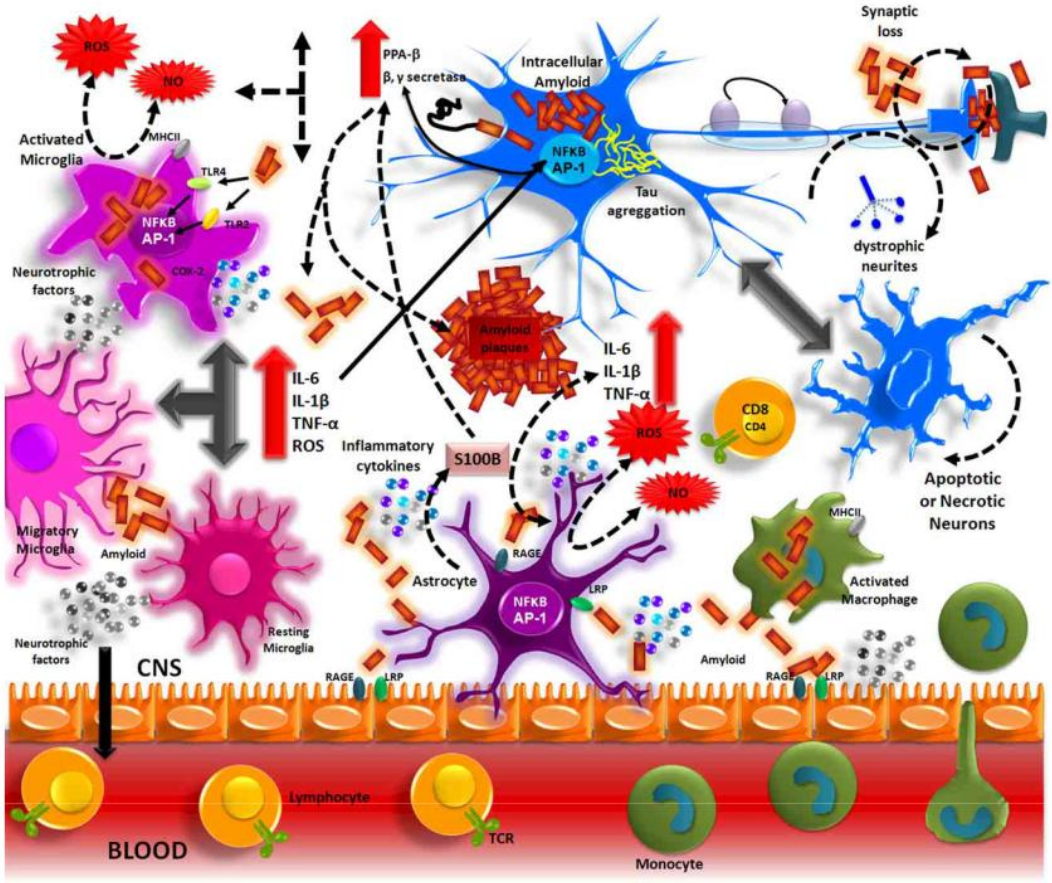

Figure 1.**Alzheimer's disease inflammation. The Aβpeptide formed by APP processing aggregates and activates microglia via TLRs and RAGE receptors. These receptors, in turn, activate the transcription factors NF-B and AP-1, resulting in the production of reactive oxygen species (ROS) and the expression of inflammatory cytokines (IL-1, IL-6, TNF). These inflammatory factors operate solely on neurons and stimulate astrocytes, which amplify pro-inflammatory signals, resulting in neurotoxicity. Inflammatory mediators produced by**

resident CNS cells stimulate the production of adhesion molecules and chemokines, which attract peripheral immune cells.

Microglia, like macrophages, recognize pathogens via pattern recognition receptors (PRRs), which also include nucleotide-oligomerization binding domain (NOD) proteins, toll-like receptors (TLRs), as well as C-type lectin synapses. To start cellular defense mechanisms, these receptors interact with pathogen-associated molecular patterns (PAMPs) or injury small molecules patterns (DAMPs) (Rubartelli and Lotze, 2008; Sterka and Marriott, 2007).As a result, the creation and discharge of ROS, pro-inflammatory cytokines (TNF-, IL-6, and IL-1)(Lue et al., 2002), chemokines (MCP1,MIP1, RANTES, and MIP1), and growth regulators like macrophage colony-stimulating factor (MCSF) and complement factors (C1q, C3, C4, and C9) (Walker et al., 1996) Microglia[51-61] can convey receptors for sophisticated numerous scavenger-type , CD40, FP receptors, Fc receptors, and glycosylation final products (RAGE), receptors in addition to the abovementioned molecules (Okun et al., 2011; Walker and Lue, 2006; Tan et al., 2000; El Khoury et al., 1999). Because even though microglia can react to various stimuli, the existence of Aβ is exceptionally crucial. Aβ causes a significant buildup of type I and II histocompatibility complex (MHC) exterior molecules (McGeer et al., 1989).Microglial cells mainly play an immunostimulatory role, expressing a wide range of immunologic reaction antigens and particles; even so, the role of microglia inside the CNS remains an open question. Microglial activation is not a one-time event; instead, it is a constant sequence of events in which microglia awakens adaptive and innate immune phagocytic immune cells and consistently[61-71] demonstrate activation via antigens on the cellular surface (Town et al., 2006). According to this principle, microglia exhibit a "variable" response, in which a mixture of the classical activation pathway and an exacerbated increase in alternative activation can be observed in Alzheimer's patients, potentially leading to irreversible damage and persistent neurodegeneration starting to cause local inflammation that may ultimately worsen neurodegeneration. The type of injury in Alzheimer's disease patients is characterized by changes in microglial morphology and astrogliosis, which is manifested by motility of astrocytes , size, and an increase in the number. In many neurodegenerative conditions,

ASTROCYTES:

astrocytes are activated, expressing high levels of nestin , vimentin, and glial fibrillary acidic protein (GFAP). Regrettably, these changes have resulted in a "disruption" of regular astrocyte actions that are required for proper neuronal function.Pathophysiologic processes include maintaining glutamate concentrations inside the extracellular environment; disrupting homeostasis causes local neuron depolarization that also leads to cytotoxic damage. As a result, while astrocytic accelerates disease progression, activation protects neurons in the brain, and intense activation exacerbates neuronal damage.Astrocytes, like microglia, respond quickly to injury; these cells are found near fibrilar Aβdeposits, which are responsible for the astroglial activation seen in Alzheimer's disease patients. Injection of Aβ oligomeric forms into the retrosplenial cortical cortex of rats resulted in significant astrocyte activation, as evidenced by transcription factor NF-kB

activation and the presence of inflammatory mediators such as cyclooxygenase-2 (COX-2) (Carrero et al., 2013),interleukin 1 (IL-α) and tumour necrosis factor (TNF-β),.Pathophysiologic processes include maintaining glutamate concentrations inside the extracellular environment; disrupting homeostatic control causes local neuron depolarization, which also gives rise to cytotoxic damage. As a result, while astrocytic activation[61-71] protects neurons in the brain, intense activation exacerbates neuronal damage and accelerates disease progression.Astrocytes, like microglia, respond quickly to injury; such cells are found near fibrilar Aβdeposits that are willing to take responsibility for the astroglial activation seen in Alzheimer's disease patients. Injection of Aβ oligomeric forms into the retrosplenial cortical cortex of rats led to a significant astrocyte activation, as evidenced by transcription factor NF-B activation and the presence of inflammatory mediators including such tumour necrosis factor (TNF-), interleukin 1 (IL-1) and cyclooxygenase-2 (COX-2) (Carrero et al., 2013).Activated astrocytes demonstrate receptor sites that bind Aβ peptides, like RAGE, receptor-like density lipoproteins, proteoglycans, and numerous scavenger receptors on one‘s cell surface (Laferla, 2014; Medeiros and Wyss-Coray et al., 2004;). As a result, activated astrocytes can end up causing convey inflammation-associated factorsand neurodegeneration such as S100β, which is likely to induce neurite outgrowth. In Alzheimer's disease patients, S100β bit of freedom with fewer dystrophic neurites (Mrak et al., 1997).NF-kB regulates chemokine and integrin secretion in rising inflammatory, astrocytes, and promotes peripheral lymphocyte infiltration response (Moynagh, 2005); this process has become an automated method, leading to neurodegeneration.

OLIGODENDROCYTES:

Even though oligodendroglia is necessary for neuron survival and features, very little is known of how Aβ reserves impact them. There have also been studies showing adjustments in white matter and myelin abnormalities in Alzheimer's disease patients (Roth et al., 2007; Kobayashi et al., 2003). Specifically, irregularities in the white case of asymptomatic familial AD patients, particularly those with PS1 mutations, have been reported (Ringman et al., 2008). Cell death was caused by the presence of Aβ in oligodendrocyte cultures. Even though anti-inflammatory[71-81] representatives could indeed inhibit cell damage, morphological changes in the cellular occur, implying that the damage cannot be reversed (Roth et al., 2006). As a result, a mouse model proved that the combination of PS1 mutations (hPS1M146V) and Aβ acquisition affect oligodendrocyte differences and function. Such anomalies can result in unusual myelin essential protein (MBP) patterns (Desai et al., 2012), which influence political oligodendrocyte equilibrium. Finally, such cells' absence of trophic support may increase neuronal vulnerability and inflammation, favoring neurodegeneration.

MOLECULAR MEDIATORS OF INFLAMMATION IN AD:

Microglial cells and astrocytes react acutely to Aβ deposition. At the same time, amyloid plaques seem to be responsible for producing and activation of inflammatory proteins, including complement factors, acute-phase proteins, chemokines, and cytokines[81-91] such as interleukin 1 (IL-1), interleukin 6 (IL-6), tumour necrosis factor (TNF-α), and

transforming growth factor (TGF-β). Such inflammatory molecular mediators have indeed been linked with several concomitant positives and negatives (Figure 2).

THE SYSTEM OF COMPLEMENTS:

The innate immunity system is an essential, potent inducer of both adaptiveimmunity andinnate. The above scheme comprises a variety of proteases and proteins that are activated in a cascade (Forneris et al., 2013), so it would seem to play an important role in neurodegenerative disorders. To recognize particular molecular trends in pathogenic organisms, the Membrane Attack Complex (MAC) is established by binding C5–C9 (Ricklin et al., 2011) mannose-binding protein, or interaction with the C3 multifunctional protein. C3 activation attracts phagocytic cells, and the complement system utilizes the C1q molecule. The complement system plays an essential role in T-helper lymphocyte distinctions during adaptive immune response (Pekkarinen et al., 2011) and T-cell efficient control.

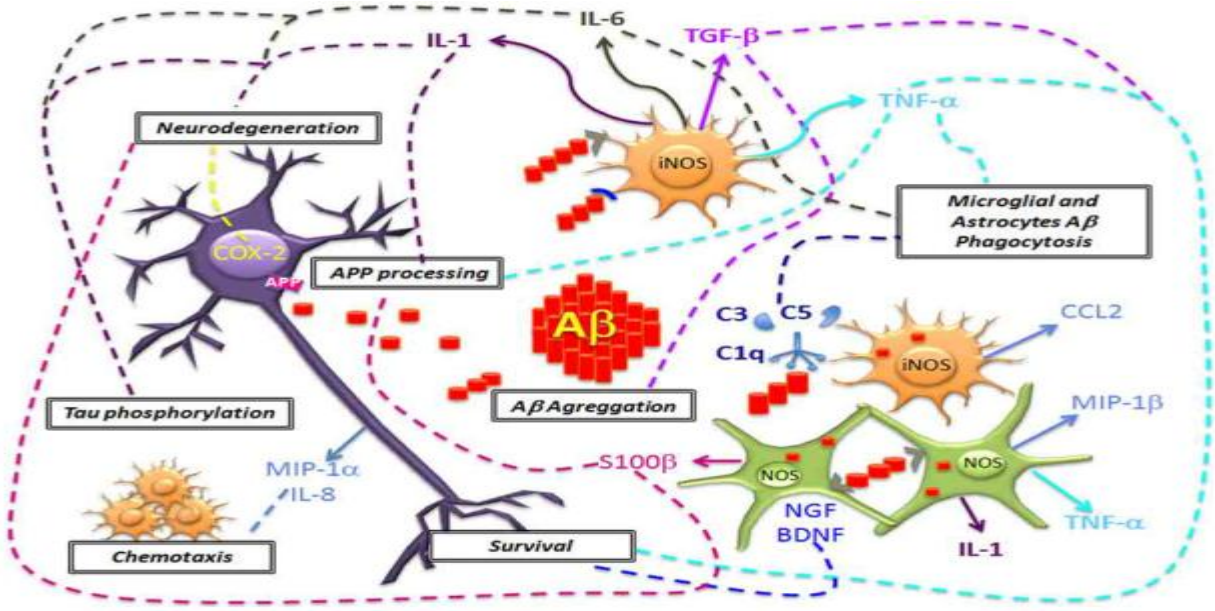

Figure. 2Neuronal damage and Aβ written statement activate astrocytes and microglia, resulting in inflammation.molecular messengers Aβclearance is mediated by the acute production of complement chemokines (CCL2, MIP-1, MIP-1, and IL-8). pro-inflammatory cytokines (IL-1, IL-6, TNF-), and system molecules (C1q, C3, and C5), However, in a chronic stage, these molecules may promote increased APP computation, Aβ deposition, Tau phosphorylation, and neurodegeneration. Another effect of glial cells in the production of NO which promotes oxidative stress. The inflammatory microenvironment promotes COX-2 production in neurons, which leads to apoptosis. Glial cells, on the other hand, have been proposed to mediate neuronal survival through the production of neurotrophic factors (BDNF and NGF) and TGF-β, but disease progression has been observed.

The classical complement pathway is dysregulated in neurodegenerative diseases. Research findings in the human brain of Alzheimer's disease patients showed a rise in the MAC surrounding senile plaques (Rogers et al., 1993; McGeer et al., 1990)and

immunoreactivity of C1q, C3b, C4d, C5b-9, and microglia surrounding **Aβ** fibrillar clusters in the microvasculature (Fan et al., 2007). The presence of the molecules in the presence of **Aβ** aggregates offers a potential connection between classical complement pathway activation, inflammation, and pathological **Aβ** aggregation. **Aβ** decrease in C1q levels has been reported in the cerebrospinal fluid (CSF) of Alzheimer's disease patients, which contrasts with an increase in C1q levels in the CNS (Smyth et al., 195). C1q recognizes fibrillar and aggregated forms of A1–43 and A1–41, but not monomeric forms, according to in vitro experiments[91-101]. Because the C1q receptor is expressed in microglia, it was thought that a rise in this particle inside the brains of Alzheimer's disease patients might affect **Aβ** phagocytosis. In central microglia rat cultural anthropology, however, exposure to A1–43 and a nanomolar concentration of C1q resulted in a decrease in **Aβ** phagocytosis compared to cultures exposed only to A1–43 (Webster et al., 2001). **Aβ** similar pattern was reported in a transgenic mouse model that conveyed mutated hAPP but did not express C1q (APPQ/). The amount of **Aβ** aggregates in such mice did not alter, but there was a decrease in glial cell activation (Fonseca). C3 is also produced by microglial cells. When these cells are exposed to **Aβ** synthetic peptides, they become activated, and their C3 synthesis increases by 5-to 10-fold (Haga et al., 1993). Whenever the dissolved form of the protein related to the complement receptor (sCrry) was overexpressed in the brain of a hAPP transgenic model, a 2- to 3-fold increase in **Aβ** deposit accounts formation takes place in one-year-old hAPP/sCrry mice, which has been preceded by extensive neurodegeneration (Wyss-Coray et al., 2003). The production of APP/C3/ double transgenic mice also revealed that molecule modulates the microglia phenotype and promotes **Aβ** degradation (Maier et al., 2009). Anaphylatoxin (C5) has been connected to excitotoxicity as well as apoptosis activation in the CNS, and this is thought to be involved in the advancement of neurodegenerative diseases. The above compound also promotes chemotaxis and the activation of glial cells. The use of C5a receptor antagonist (C5aR or CD88) in Alzheimer's disease animal studies decreases the amount of **Aβ** aggregates and hyperphosphorylated tau protein (Fonseca et al., 2009; Ager et al., 2010). It has seemed that complement system activation in Alzheimer's disease may have positive effects on **Aβ** clearance; even so, this activation may become deregulated and favor neurotoxic effects by promoting unwanted inflammation. More research is necessary to clarify the changes affecting the complement system in AD development for these reasons.

CYTOKINES:

Cytokines, which are small proteins that mediate inflammation, can be produced by immune system cells. Microglial cells and astrocytes generate cytokines inside the CNS that also play an important role in CNS development during the embryonic stages. Cytokines play a role in the inflammatory processes that occur in neurodegenerative diseases. Such proteins could play a role in the pathology's development in Alzheimer's disease. Pro-inflammatory cytokines such as IL-10, TGF-β , TNF-α, IL-6, and IL-1, are associated with higher AD patient tissues and CSF (Jiang et al., 2012; Tarkowski et al., 2003; Blum-Degen et al., 1996 Mrak, and Griffin, 2006;). The rise in such cytokines is connected to microglia activation caused by Aβ aggregate particles (Meda et al., 1999). Overexpression of the mutant hAPP protein in animal studies has shown a direct relationship

between the[101-111] amount of Aβ aggregate particles and elevated IL-1 ,TNF-α, IL-12, IL-1, and IL-6 levels (Patel et al., 2007). Specifically, research has been conducted to determine the relationship between each cytokine and AD.

IL-1:

IL-1 has been shown to induce APP-mRNA appearance in endothelial cells (Goldgaber et al., 1990), suggesting that an increase in IL-1 in AD patients may be linked to Aβ formation. In a study with Alzheimer's patients, it was also proposed that IL-1 was produced by microglial cells surrounding NPS, and this cytokine could promote S100 synthesis in atrocities (Griffin et al., 1990). Following that, it was discovered that IL-1 was a factor in initiating dystrophic neuritis formation in Aβ diffuse deposits (Griffin et al., 1996). Correspondingly, S100 stimulates the formation of dystrophic neuritis and the expression of APP-mRNA in primary cultures of rat cortical neurons (Li et al., 1999). Thus, IL-1 may promote Aβ formation and neuronal degeneration via S100, which is found in neurons[112-121]. Furthermore, an increase in IL-1 in Alzheimer's disease patients may promote an increase in p38-MAP kinase activity, leading to Tau hyperphos-phorilation (Sheng et al., 2000; Li et al., 2004). Blocking IL-1β signaling reduces GSK-3 activity and Tau phosphorylation while promoting neurogenesis via the Wnt/-catenin pathway (Kitazawa et al., 2012). However, it has recently been proposed that IL-1β could promote A removal (Matousek et al., 2013).

IL-6:

IL-6 is generated by microglia cells and therefore is engaged inside the immunoreactivity found in clinical dementia patient tissues (Hull et al., 1997. IL-6, like IL-1, promotes APP expression and may contribute to NFT creation by inducing Tau phosphorylation via cdk5/p36 pathway deregulation (Ringheim et al., 1999). (Quintanilla et al., 2005). IL-6 overexpression, on either hand, has been observed in the brains of two hAPP transgenic models (TgCRND9 and Tg2654). This overexpression caused considerable gliosis, a decline in Aβ deposits in TgCRND9 mice human brain due to phagocyte marker up-regulation in glial cells, and an increase in microglia Aβ phagocytosis.

TNF-α:

TNF-α is a cytokine that can be beneficial or detrimental to various neurons. This transcription factor stimulates the NF-B transcription factor that also promotes the interpretation of pro-inflammatory atoms and the synthesizing of neuronal survival factors including cabining, manganese superoxide dismutase enzyme, and anti-apoptotic Bcl-2 protein (Wajant et al., 2004; Kamata et al., 2006). This cytokine can activate microglia glutamines, causing excitotoxicity and promoting the development of neurodegenerative diseases (Takeuchi et al., 2007). The direct role of this cytokine in AD is unknown; however, TNF- may be associated with increased - and –secretase enzyme expression (Blasko et al., 2001; Liao et al., 2005).TNF-α has been seen in vitro to cause and[121-131] effect BACE1 interpretation, favoring APP processing (Yamamoto et al., 2007). Soluble TNFα-inhibitors protected against APP deregulation by reducing amyloidal overall total creation and attenuating cognitive impairment in 3xTgAD mice exposed to chronic ancillary inflammation (McAlpine et al., 2009). Long-term inhibition of the TNF- receptor signal transduction pathway, on the other hand, can impair microglia ability to efficiently remove

Aβ aggregates, favoring its agglomeration in the initial stages (Montgomery et al., 2011).

TGF-β:TGF-β; seems to be another cytokine with pleiotropic functions, as it inhibits apoptosis and promotes neurogenesis. This cytokine is associated with neurodegenerative diseases (Konig et al., 2007; Krieglstein et al., 2003;). TGF-1 levels have been found to be higher in the brains of Alzheimer's disease patients (Flanders et al., 1996). TGF-β1 overexpression promotes amyloidogenesis in the nerves as well as cerebral vasculature in early stages (3–4 months) in animal models (hAPP/TGF-β1) (Wyss-Coray et al., 1998). In contrast, there is a decline in amyloid plaque forming in the parenchyma of hAPP/TGF-β1 transgenic mice, which also correlates with microglial activation (Wyss-Coray et al., 2002). Although TGF levels are elevated in AD patients, there is a significant decrease in the representation of the TGF-β receptor type II (TRII); this decrease may indicate that the signalling pathway mediated [131-141]by this receptor has important neuroprotective features but may be changed during the disease's progression (Tesseur et al., 2007). In conclusion, the role of cytokines remains an open question. On the one hand, cytokines may promote Aβ phagocytosis and neuronal survival by activating microglia and astrocytes. Chronic cytokine manufacturing, on either hand, has been linked to neurodegeneration.

CHEMOKINES: Chemokines are protein molecules that entice monocytes, macrophages, lymphocytes, neutrophils, basophils, eosinophils, and dendritic cells to sites where an immune reaction is needed. Chemokines are classified into four families based on the activation of their G protein-coupled receptors: CX3C , CC, CXC, and C, (Wells et al., 1998; Cyster, 2000).astrocytes but instead microglial cells are the primary chemokine producers in the CNS, and their receptors have been found in neurons. Chemokines, as well as one's receptors, also play a role in the CNS immune reaction, promoting lymphocyte flow of migrants from lymphoid organs to initiate the inflammatory process (Ransohoff et al., 1997).The existence of monocyte chemotactic proteins (CCL2 OR MCP-1) and chemokine receptors CCR5 and CCR3 in reactionary microglia surrounding senile plaques in AD patients is proof chemokine involvement. In comparison, the monocyte inflammatory protein 1 (MIP-1) is primarily found in neurons, while MIP-2 is found mainly in the astrocytes that encircle the plaques (Ishizuka et al., 1999; Xia et al., 1999). The expression patterns of chemokines and their receptors promote glia-neuron communication in establishing a local inflammatory reaction, which might also favor Aβ phagocytosis in the initial stages of Alzheimer's disease. Similarly, it is well recognized that this inflammation contributes to Tau pathology and thus hastens the progression of the disease (Zilka et al., 2013). The inflammatory process in Alzheimer's disease promotes phagocytic cell chemotaxis, favoring microglial recruitment around A aggregate particles (Yamamoto et al., 2006). Aβ recent research on CSF from Alzheimer's disease patients found elevated CCL2 levels directly linked with cognitive impairment (Westin et al., 2013). Furthermore, Aβ agglomeration causes an increase in IL-8 (CXCL8) production in neurons, which also correlates with just a rise in the creation of brain-derived neurotrophic factor (BDNF) (Ashutosh et al., 2012). The existence of Aβ in the microvasculature stimulates the release of MIP-1β , MIP-1α, MCP-1, and IL-8, chemokines, promoting monocyte distinction

into the macrophages and migration across the blood-brain barrier (Fiala et al., 1998). IL-8 and MCP-1β chemokine stages were also higher in the CSF of Alzheimer's disease patients (Galimberti et al., 2004; Correa et al., 2012). Similarly, in vitro models had also displayed the capability of lymphocytes (CD8+ and CD4+) to migrate through[141-151] the blood-brain barrier due to increased MIP-1 levels (Man et al., 2009). Finally, chemokines in the CNS can encourage regional and tangential immune response cellular proliferation to initiate an immune response. It has been proposed that chronic chemokine production contributes to AD.

CYCLOOXYGENASES: Chemokines are small proteins that attract dendritic, monocytes, eosinophils, macrophages, neutrophils, lymphocytes, basophils, and monocytes cells to sites where an immune reaction is required. Chemokines are classified into four families based on the activation of their G protein-coupled receptors: CX3C, CC, CXC, and C. (Wells et al., 1999; Cyster, 2000). Glial cells and microglia are the primary chemokine producers in the CNS, and their receptors have been found in neurons. Chemokines, as well as their neurotransmitters, also play a role in the CNS immune system, promoting lymphocyte migration from lymphoid organs to initiate the inflammatory reaction (Ransohoff et al., 1997). The existence of monocyte chemotactic proteins (MCP-1α or CCL2) and chemokine receptors CCR3 and CCR5 in reactionary microglia surrounding geriatric plaques in AD patients indicates that chemokine involvement. In comparison, the macrophage inflammatory protein 1 (MIP-1β) is now primarily found in neurons, while MIP-2β is primarily found in the astrocytes that encircle the inscriptions (Xia et al., 1999; Ishizuka et al., 1998;). The expression patterns of chemokines and one's neurotransmitters promote glia-neuron interaction to establish a local inflammatory response, which may favour Aβ phagocytosis in the early stages of Alzheimer's disease[141-151]. Similarly, it is well recognized that this inflammation appears to contribute to Tau pathology and thus hastens disease progression (Zilka et al., 2012).Chronic inflammation in Alzheimer's disease encourages phagocytic cell chemotaxis, favoring microglial recruitment around **Aβ** aggregate particles (Yamamoto et al., 2007). A new analysis of CSF from Alzheimer's disease patients found elevated CCL2 levels that also correlated with cognitive impairment (Westin et al., 2013). Furthermore, Aβagglomeration causes an increase in IL-8 (CXCL8) production in neurons that also connects with just a rise in the creation of brain-derived neurotrophic component (BDNF) (Ashutosh et al., 2021). The existence of Aβ in the microvasculature promotes the release of MIP-1β , MIP-1α, MCP-1, and IL-8, chemokines, announcing monocyte distinction into macrophages and migration across the blood-brain barrier (Fiala et al., 1999). IL-8 and MCP-1α chemokine levels were also higher in the CSF of Alzheimer's disease patients (Correa et al., 2012; Galimberti et al., 2004;). Correspondingly, in vitro models have shown the ability of lymphocytes (CD8+ and CD4+) to migrate through to the blood-brain barrier due to increased MIP-1α levels (Man et al., 2008). Finally, chemokines in the CNS can encourage regional and peripheral immune system[151-161] cellular proliferation to initiate an immune response. It has been proposed that chronic chemokine production contributes to AD.

CYCLOOXYGENASES: Cyclooxygenases (COX) are enzymes that convert arachidonic

acid to H2 prostaglandin, a PG precursor. These lipidic molecular mechanisms are involved in inflammation overall even though they end up causing vasodilation, enabling immune response cell transport to occur just at the target site (Williams, 1979). The mammalian brain expresses COX-2 and COX-1 isoforms. COX-1 is conveyed in microglia and neurons that undertake independent sensory features in the pons and spinal cord. COX-2 is found in glutamatergic neurons of a cortex and hippocampus and is believed to be involved in the regulation of elastic-plastic procedures and long-term stimulatory effects (Yamagata et al., 1995; Breder et al., 1996); in pathological conditions, the existence of COX-1 in the CNS is affiliated to inflammatory advancement, whereas COX-2 is affiliated with neurotoxicity. In Alzheimer's disease patients, the microglia surrounding the NPS express a high level of COX-1, implying inflammation (Yermakova et al., 2000). COX-2 utterance in the hippocampal CA3 region, on the other side, probably relates to the number of NPs and NFTs and the identified cognitive decline (Ho et al., 2002). COX-2 overexpression in a triple transgenesis model (hAPP/PS1/hCOX-2) increased active Caspase-3 immunoreactivity and neuroblastoma protein.The Rb protein controls the G1 phase of the cell, and yet phosphorylation at S813 inhibits cellular proliferation. In vitro study showed that hCOX-2 upregulation accelerates the apoptotic damage caused by A in primary cultures of cortical and hippocampal nerve cells deduced from transgenic mice causing cell cycle abnormalities (Xiang et al., 2003a). COX-2 also facilitates the growth of amyloid plaques in the parenchyma and stimulates the amount of prostaglandin E2. This increased plaque creation is linked to increased amyloid peptide formation (A2–50 and A1–52) via – protease activation but has no effect on APP expression levels (Xiang et al., 2003b). Studies in an animal model using COX-2/ deficient mice revealed that the inflammatory reaction mediated by A was reduced, implying that COX-2 inhibition can be an essential objective to be pursued. The assessment of post-mortem brain from Alzheimer's patients revealed that the highest immunoreactivity for COX-2 and ppRb occurred in the early stages of the disease (Braak), before the highest stromal cells and microglial stimulation. In contrast to in vitro findings, post-mortem tissue analysis did not support a direct link between microglial and process comprises activation and neuronal COX-2 and ppRb expression in AD (Hoozemans et al., 2006). The reason for changes in COX-2 levels and during various stages of Alzheimer's is currently unclear. However, it’s been recommended[151-161] that inflammatory response in the early stages of Alzheimer's disease may promote such changes and that IL-1 may promote a rise in COX-2 expression and PG manufacturing (Hoozemans et al., 2002).

NITRIC OXIDE: NO is a chemical compound that plays a significant role in cell signalling. L-arginine is transformed to L-citrulline, and NO is released in the oxygen in the air. The enzyme is responsible for catalyzing this response is nitric oxide catalytic subunit (NOS), which comes in isozymes. The neuronal isoform (nNOS) is found in neurons, astrocytes, and blood vessels throughout the CNS. Endothelial isoforms of nitric oxide synthase (eNOS) are found in forebrain pyramidal neurons, endothelial cells, and some astrocytes. The inducible homolog (iNOS) is usually expressed at low concentrations, although it is

upregulated in microglia during neuroinflammation. Under physiological conditions, NO is thought to regulate neurotransmission and estrogens release, as well as encourage cell viability and lengthy potentiation. However, in inflammatory diseases, high levels of NO are produced, which may contribute to synaptic transmitting dysfunction, protein, and fatty acid oxidative damage, leading to oxidative stress, and neuronal death (Calabrese et al., 2008, Bishop and Anderson, 2006; Liu et al., 2003;). Tissue but instead neuronal assessments of Alzheimer's disease patients showed that A could promote NOS expression and NO production in microglial cells and reactive astrocytes (Goodwin et al., 1998; Wallace et al., 1998; Akama et al., 1999). **A** also stimulates the release of the pro-inflammatory cytokines IL-1 and TNF, which contribute to the emergence of NO and peroxynitrites[161-171] (Rossi and Bianchini, 1996; Combs et al., 2001) and end up causing protein and lipid modifications, mitochondrial damage, apoptosis, and promote **Aβ** formation by increasing the -secretase complex activity (Torreilles et al., 1999; Keil et al., 2004; Guix et al., 2012).

TREATMENTS FOR INFLAMMATION MODULATORS: THERAPEUTICS IN AD:

In the early 1991s, research findings started to emerge linking the inflammatory reaction to Alzheimer's disease. Fillit et al. (1992) discovered that some pro-inflammatory cytokines had been raised in Alzheimer's patients. Observational data (Li et al., 1993) indicate that people with arthritis have a lower incidence of Alzheimer's disease. It has been postulated that such a negative association might be linked to the long-term use of anti-inflammatory prescription medications (Dickson and Rogers, 1994). Based on these and many other findings, these drugs were considered a novel therapeutic approach for Alzheimer's treating diseases. Numerous epidemiological studies, experimental in vitro and in vivo models, and clinical trials are currently underway to elucidate the relationship between inflammation modulators and Alzheimer's disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are two types of anti-inflammatory drugs. The above section will go over the mechanisms of action of both kinds of anti-inflammatory drugs, one's role in Alzheimer's disease, [171-174]and the findings of the most important experimental and epidemiological studies. The above section will also look at passive and active immunotherapy as a treatment strategy for Alzheimer's disease (Table 1).

ANTI-INFLAMMATORY DRUGS

NSAIDs are a diverse class of drugs with a similar mechanism of activity involving preferential or non-selective inhibition of COX-1 and COX-2 enzymes (Vane and Botting, 1988). Such enzymes catalyze the acid is converted to prostaglandin H2 (PGH2), which is then transformed into various PGs (PGE2, PGD2, PGF2, and PGI2) as well as thromboxane (TX) (Dubois et al., 1999). When tissue damage occurs, PG and TX synthesis rise, acting as inflammation mediators, increasing blood flow and vasodilation in the damaged tissue, and rising microvascular permeability (Flower et al., 1977). Several epidemiological studies designed to identify AD risk factors have found that long-term use of NSAIDs may reduce the risk of AD. The following are the findings of some of the most representative studies. According to the Sydney Old Individuals Study, NSAID use has been

substantially lower in subject areas that evolved Alzheimer's disease than in those who did not grow whatever form of dementia during the study period (Broe et al., 2001). Notably, NSAID use is not linked to any form of dementia but apart from Alzheimer's. This finding suggests that NSAID use in Alzheimer's disease may work through a different method than their properties as cyclooxygenase inhibitors. The Rotterdam research (In'T Veld et al., 2002), the Multi-Institutional Study Alzheimer's Genetic Epidemiology Study (Yip et al., 2006), as well as the Canadian Study of Health and Aging (CSHA) (Coté et al., 2013) all found a link between NSAID use and a lower risk of Alzheimer's disease. . Szekely et al. performed a conceptual of six studies (the Baltimore Longitudinal Study of Aging, the Cache Township Study, the CSHA, the Cardiovascular Health Study, the Framingham Heart Study, and the Monongahela Valley Independent Elders Study). They confirmed the link between NSAID use, including a lower risk of Alzheimer's disease (Szekely et al., 2009). A few studies, however, have failed to replicate this association. The Longitudinal Aging Research Amsterdam discovered a reduction in Alzheimer's associated risks with aspirin alone, but no association between Alzheimer's risk and other NSAIDs (Jonker et al., 2005). Bendlin et al. also found no significant differences in neuropsychological learning and memory tests between NSAID users and non-users (Bendlin et al., 2011). Both these researchers have found conflicting results, such as Fourier et al., who discovered a link between NSAID use and a drop in Mini-Mental State Examination (MMSE) scores (Fourrier et al., 1997). Correspondingly, Breitner et al. discovered a higher prevalence of AD among many NSAID users when compared to the control group (Breitner et al., 2010).Once Martin et al. tested the effects of naproxen and celecoxib in older individuals with such a family background of AD, they found similar unfavorable results (Martin et al., 2009). In just this study, topics given naproxen or celecoxib performed worse on the MMSE than those given a placebo, indicating that all these drugs harm cognitive performance. Aisen et al. investigated the effects of rofecoxib and naproxen on patients with mild to mitigate Alzheimer's disease (Aisen et al., 2005). Only one researcher showed no significant differences in performance between treated patients with rofecoxib, naproxen, or placebo. Furthermore, subject matters in the Opiate painkiller organizations experienced a greater frequency of adverse effects, including such fatigue as well as dizziness, as well as a significantly higher prevalence of hypertension. Another study on rofecoxib in patients with mild cognitive impairment (MCI) discovered a negative effect (Thal et al., 2006). The findings of AD animal study research have seemed to support the notion that NSAID use is advantageous not just as a disease prevention strategy but also as a therapeutic strategy. This assistance was seen in Tg2576 (Swe-APP) transgenic treated mice with indomethacin, which also resulted in a significant decrease in A levels (Aβ1-41 and Aβ1-42) both in cortex and the hippocampus (Sung et al., 2006).Following that, Joo et al. demonstrated that mice handled in tablet dosage form for three weeks after being treated with Aβ1–43 or expressing Swe-APP regained performance comparable to the Morris liquid maze test in a car group (Joo et al., 2007). Coma et al. acquired similar results in Tg2676 transgenic mice treated to Triflusal (a salicylate-family NSAID but it’snot an aspirin derivative), re-establishing transgenic mice (Tg+) achievement in the Mccoy test and

a conditional test (Coma et al., 2011). Even though Triflusal did not affect NP size (NPS) or number, it did reduce the number of enabled astrocytes and microglia and the tiers of IL-1β and TNF-α in the hippocampal CA1 area and entorhinal cortex. Van Dam et al. discovered similar results.Treatment with ibuprofen for 3 months reduced the inflammatory reaction inside the animal model (5XFAD), which overexpressed the Swedish double mutated gene (M761L , K760N), Florida mutation (I717V), London mutation (V1717), and PS1 double mutation (M641L and L682V). There's a rise in dissolved Aβ42 levels and perhaps some changes in behavior, raising questions of whether anti-inflammatory drug use has been beneficial for AD treatment (Hillmann et al., 2013).

Table 1: Treatments for inflammation modulation and their effects in animal models and clinical trials

Drug	**Effects in animal models and clinical trials**
Anti- tau antibodies	In treated mice, there was a decrease in the number of NFTs.
Celecoxib	Drug-treated group was found to score lower than placebo-treated group in cognitive tests, in clinical trials
Tau peptides	In mouse model studies, there was a reduction in the number of NFTs and a prevention of cognitive decline.
Rofecoxib	There have been no reported benefits. In clinical trials, there is a high frequency of adverse effects in the drug-treated group.
Triflusal	In mice treated with this drug, there was a decrease in microglial and astrocytic activation, as well as a decrease in cytokine levels.
Anti-Aβ antibodies	A decrease in synaptic loss and the number of dystrophic neurites, as well as an increase in the number of dendritic spines, have been observed in treated mice. There have been no reported positive effects in clinical trials.
Aβ peptides	This therapy was effective in preventing synaptic loss in mice. Although clinical trials have shown some benefits in subjects who developed antibodies, the incidence of meningoencephalitis as a side effect is alarmingly high
Corticosterone/ Dexamethasone	Cortex, cerebellum and brainstem from mice treated with this drug showed increased expression of APP and beta-secretase, Aβ deposition, tau aggregation and caspase 3, cytochrome c, IL-1 and TNF-α levels. Drug-treated mice were found to score lower than placebo-treated mice in memory tasks
Prednisone	No beneficial effects reported. Higher frequency of behavior disturbances was observed in the drug-treated group, in clinical

	trials
Dexamethasone	This drug increased the expression of APP and beta-secretase, A deposition, tau aggregation and caspase 3, cytochrome c, IL-1, and TNF- levels in the cortex, cerebellum, and brainstem of mice. In memory tasks, drug-treated mice performed worse than placebo-treated mice.
Ibuprofen	Lower A levels in the cortex and hippocampus were observed in mice treated with this drug.
Mefenamic acid	In cognitive tests, mice given this drug performed as well as healthy controls.
Therapy	NSAIDs+ Glucocorticoids+ Immunotherapy
NSAIDs	Naproxen+ Celecoxib+ Rofecoxib+ Indomethacin+ Mefenamic acid+ Triflusal+ Ibuprofen
Glucocorticoids	Corticosterone/ Dexamethasone + Prednisone
Immunotherapy	Aβ peptides+ Anti-Aβ antibodies+ Tau peptides+ Anti-tau antibodies

GLUCOCORTICOIDS: Glucocorticoids, like NSAIDs, have potent anti-inflammatory effects, making them promising candidates for Alzheimer's disease treatment. Glucocorticoids' mechanism of action is based on their ability to bind to their receptor sites (Glucocorticoid Receptor, GR), which is found in the cytoplasm in its free form and translocates into the nucleus after shackling to one of its ligands. When GR enters the nucleus, it works by binding to specific nucleotide sequences known as glucocorticoid specific receptors (GREs), which are found in the gene promoter of many genes. GR will either negatively or positively regulate the expression depending on what type of GRE series with which it binds (Beato et al., 1990). The importance of this adhesion in the inflammation reaction is that specific genes that GR binds to and activates, such as annexin-1 (lipocortin-1), interleukin 10, and NF-B inhibitor (IkB-α), possess anti-inflammatory effects (Barnes, 2008).

Furthermore, this has been proposed that glucocorticoids interact directly with Aβ. The existence of NPs in comment AD brains was observed to be decreased in subjects who received persistent corticosteroid remedies. There was no statistically meaningful difference between the number of NFTs. This study also found no link between chronic NSAID treatment and the number of NPs (Beeri et al., 2013). Even though its anti-inflammatory impact, glucocorticoids as a therapeutic strategy in the treatment of Rheumatoid arthritis is controversial, even though countless studies link elevated levels of glucocorticoids (cortisol) to a higher risk of Alzheimer's disease. Swaab et al. evaluated cortisol tiers in post-mortem CSF samples in 1995 and found an 90% rise in AD subjects compared with healthy controls (Swaab et al., 1995). These findings are in line with the observations of Laske, who discovered significantly higher rates of serum cortisol in Alzheimer's disease patients when compared to the time of life healthy controls (Laske et al., 2010). A large percentage of animal model experimentations do not endorse

corticosteroids as a treatment approach for Alzheimer's disease and suggest that these drugs encourage the growth of the disease's neuropathological characteristics. The administration of glucocorticoids (corticosterone and dexamethasone) to rats leads to an increase in APP affirmation in the cortex, cerebellum, and brain stem (Budas et al., 2000), implying a negative impact.
Furthermore, there is an increase in A forming due to the increased APP and -secretase levels. These glucocorticoid tiers are also linked to Tau buildup (Green et al., 2006), memory and learning impairment (Yao et al., 2007), and elevated levels of caspase three and cytochrome c, indicating a pro-apoptotic environment (Li et al., 2010). Finally, high corticosterone levels in hippocampal cells have a pro-inflammatory effect, favoring the utterance of IL-1 and TNF-α (Macpherson et al., 2005).

IMMUNOTHERAPY: There's presently no consensus among experts as to what causes AD pathophysiology or even which occurrences are reasons but which are bodily reactions to help counter the disease's damage. This issue has been raised concerning inflammation. So although therapies based on NSAIDs and glucocorticoids were developed on the assumption that now the immune reaction in AD is detrimental (Blasko et al., 2005) or may be a causal factor (McGeer and McGeer, 1996), both these considerations assume that the inflammatory system could be beneficial because it attempts to counteract the harmful effects of A oligomers and Tau aggregation. Immunotherapy is among the treatment interventions developed on such foundations since it is based on stimulating the immune reaction against the altered compounds found in the disease's most unusual histopathological lesions (NPS and NFTs) and destroying them. This segment will go over the different types of immunotherapy (anti-Aβ and anti-Tau immunotherapy) and some of the outcomes of immunotherapeutic studies with Alzheimer's disease patients.

CONCLUSION: Several hereditary and epidemiological research findings have also currently given an outline of the inflammatory mechanisms at work in Alzheimer's disease. Even though the molecular mechanisms of the disease are unidentified, Aβ induced inflammatory response plays a significant role in the neurodegenerative process. Microglial and astrocytic activation drives the inflammatory reaction by inducing pro-inflammatory molecules and linked signalling pathways, resulting in synaptic damage, neuronal loss, and the activation of other inflammatory participants. Even though the involvement of amyloid as a possible future originator of inflammation is unclear, its buildup has an indirect impact by activating caspase activation and transposable elements like NF-kB and AP-1, which also produce a slew of inflammation amplifiers like IL-β1, TNF-α, and IL-6. TNF-α, IL-1, and IL-6 are pro-βinflammatory cytokines that can act directly on neurons to end up causing apoptosis.
Similarly, TNF- and IL-1 can stimulate astrocytes, which could also discharge factors that activate microglia. Moreover, NF-kB controls the expression of APP, BACE1, and PSEN. The genes encoding these proteins contain NF-B-recognized sites in their promoter regions, and the presence of pro-inflammatory cytokines increases the expression of these factors. Inflammatory mediators that behave on neural activity increase amyloid production and activate microglia-mediated inflammation. The interaction between microglia and neurons

increases the production of aspects that influence AD-type pathology. The neural reaction, on the other hand, is precise to the receptor - associated conveyed in the various neurones. TNF-α, for example, binds TNFR1, which activates the cell growth pathway via NF-kB and the apoptotic pathway via caspase activation. TNFRII signalling, on the other hand, only activates NF-kB. The pro-inflammatory cytokine IL-1β, expressed by microglial cells, is the primary mediator of this cascade. IL-1β may end up causing neuronal death via a number of routes, that also activate microglia and increase IL-1β discharge, resulting in a self-sustaining method that is magnified by itself. This slow but steady inflammatory state, which occurs in the brain over long periods, can eventually destroy neurons and contribute to the clinical symptoms noted in the disease (Figure 1). Ultimately, in light of all of the preceding data, and especially so because results of the treatments utilized have indeed been contradictory thus far, and there are no clinical trials that show that anti-inflammatory therapies and the use of immunotherapy are wholly safe or beneficial, new tactics for AD immunological treatments must be developed and implemented.

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