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REVIEW ARTICLE

Inflammation Drives Alzheimer's Disease: Emphasis on 5-lipoxygenase Pathways

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Abstract: It is a known fact that inflammation affects several physiological processes, including the functioning of the central nervous system. Additionally, impairment of lipid mechanisms/pathways have been associated with a number of neurodegenerative disorders and Alzheimer's Disease (AD) is one of them. However, much attention has been given to the link between tau and beta-amyloid hypothesis in AD pathogenesis/prognosis. Increasing evidences suggest that biologically active lipid molecules could influence the pathophysiology of AD *via* a different mechanism of inflammation. This review intends to highlight the role of inflammatory responses in the context of AD with the emphasis on biochemical pathways of lipid metabolism enzyme, 5-lipoxygenase (5-LO).

Keywords: Alzheimer's Diseases, 5-lipoxygenase, Neuro Inflammation, Neurodegeneration, Lipid Molecule, Arachidonic Acid.

1. INTRODUCTION

Alzheimer's Disease (AD) is a destructive neurodegenerative disease and a leading cause of dementia in the elderly population that declines memory functions, decision making, reasoning ability, weakens cognition, and causes changes in behavior. In 2019, it was estimated by Alzheimer's disease international that 50 million people are living with dementia, a figure which may rise up to 152 million by the year 2050 [1].

The two classic major pathological hallmarks of AD include amyloid-beta (Aβ) accumulation and neurofibrillary tangles (NFTs) formation [2]. Some new pathogenic biomarkers have shown up which makes it even more challenging to slow down the progression of AD. Soluble amyloid β peptide (Aβ) is build up at an early stage that initiates various faulty cycles like a decline in synaptic communication, ruptures mitochondria, and enhances oxidative stress that causes sustained endoplasmic reticulum (ER) related stress reaction [3]. Other pathological hallmarks of AD, which were initially described by Alois Alzheimer, is the higher occurrence of 'lipoid granules' or 'adipose inclusions' suggesting dysregulated lipid metabolism [4]. Inflammation, on the other hand, is a component of initial innate response that engages immune cells to the spot of stress mainly through the chemotactic function of activated chemokines. Furthermore, the dual involvement of chemokines as pro and anti-inflammatory is well evident and must be considered for both clinical and immunopathological approaches in AD [5, 6]. Eicosanoids are the signaling molecules and inflammatory mediators that are generated in the pathway of Arachidonic Acid (AA) metabolism mediated by 5 lipoxygenases (5-LOs) [7]. These biologically active lipid molecules could manipulate the working of the central nervous system (CNS) as well as the pathophysiology of neurodegenerative disorders, such as AD, *via* various mechanisms involved in classical inflammation and are discussed here.

2. ALZHEIMER'S DISEASE AND AGING

A large number of cases of AD are sporadic, without any regular genetic expression among different cases. In 2019, Alzheimer's Association stated that the signs and symptoms of AD typically become diagnosable only between the age of 65-74 years (3%), 75-84 years (17%), and ≥ 85 years (32%) [1, 2].

Generally, the aging brain is correlated with the high risk of chronic neurodegenerative mechanisms involved in disease progression [8, 9]. In this view, the biochemical pathways suggest that brain aging is associated with the activation of microglia and persistent brain inflammation results in neuronal death [10]. Patients with AD go through remarkable disintegration of neurons, as a result of an extracellular aggregation of Aβ peptide and intracellular aggregation of tau protein that leads to the formation of neurofibrillary tangles [11, 12]. Additionally, it has become evident by the

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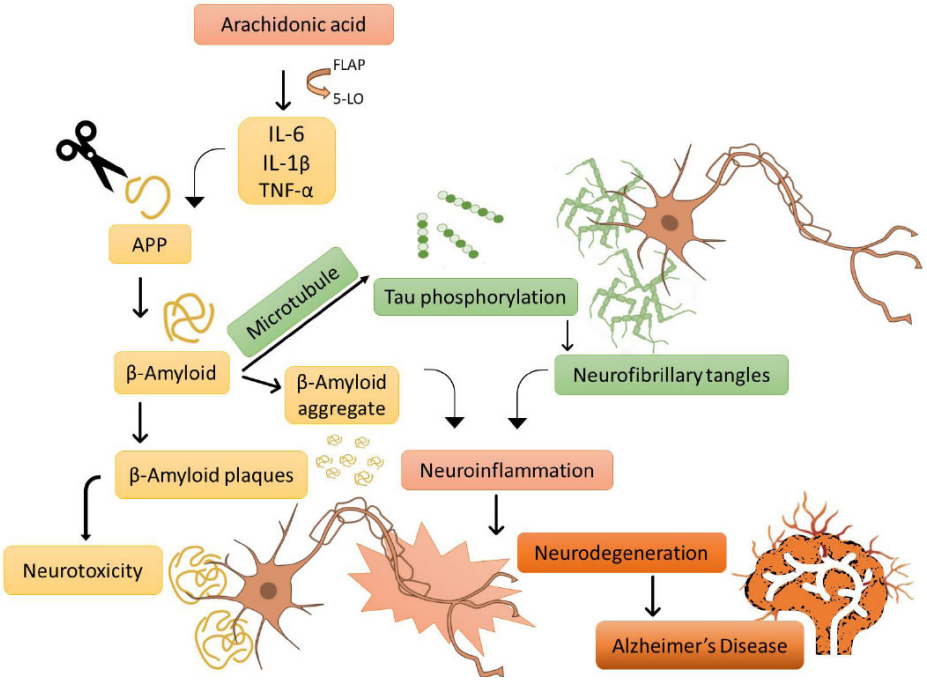

Fig. (1). Association of 5-Lipoxygenase enzyme (5-LO) in progression of Alzheimer's disease. FLAP- 5-Lipoxygenase activating protein, IL- Interleukin, TNFα- Tumour Necrosis Factor alpha, APP- Amyloid Precursor Protein. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

different published studies that levels of 5-lipoxygenase(5-LO) and its metabolites increase age dependently [13, 14]. Therefore, aging and involvement of 5-LO have been considered as potential risk elements for the progression of AD [15, 16].

3. MECHANISM INVOLVED IN THE DEVELOPMENT OF ALZHEIMER'S DISEASE

Scientific developments over the past decades have expanded the understanding of cellular and molecular aspects of AD (Fig. **1**). In spite of that, AD remains mainly idiopathic, therefore, treatments and therapies meant to battle the disease progression successfully are still lacking. Studies understanding the initiation, progression, and prevention of AD and its related conditions are limited. Emerging data indicates that the healthy physiological interactions between neurons, astrocytes, microglia, as well as vascular cells are prerequisites for proper brain functioning. Early diagnosis and therapy can help in protecting neural circuits from damage, but it may get worse if not treated properly [17].

3.1. Amyloid β Plaques

The irregular breakup of Aβ protein is involved in Aβ related pathology that gives rise to monomeric form and later on accumulates to form oligomeric Aβ. These Aβ monomers combine with each other and form Aβ plaques and fibrils [18]. The role of Amyloid precursor protein (APP) is still unclear, but it is expected to be responsible for cell growth [19]. Generally, non-amyloidogenic APP proteolysis takes place with the help of α- secretase or γ-secretase resulting in the formation of dissoluble fragments [20]. Whenever γ secretase and faulty β-secretase over-activate the cleavage of APP, it results in the formation of insoluble peptides of Aβ, which accumulate to form Aβ plaques in the brain and outside the neurons [21-26]. The exact function of Aβ in the pathology of AD is still an unsettled question as plaques of Aβ may aggregate for up to 10 years without any detectable symptoms or diagnosis of AD, thus, being the reason for the development of AD in the aged population.

3.2. Tau Protein and Neurofibrillary Tangles

The presence of NFTs emerges mainly after the tau hyperphosphorylation. It is a microtubule linked protein that secures microtubule and its hyperphosphorylation initiated AD pathology [27, 28]. In the case of AD, phosphorylation of tau protein takes place at numerous sections leading to the elimination of tau from the microtubule. This results in the shrinking of microtubule and interrupting various cellular functions [29-31]. Moreover, hyper-phosphorylation of tau results in its accumulation into coiled fragments that ultimately give rise to NFTs [32-36]. Tau tangles aggregation and the weakened cellular actions cause failure in neuronal structure and nutrient transport, leading to the death of neurons [30]. So far, major approaches were made to target the inhibition of Aβ plaques and NFTs, which failed in clinical trials. Therefore, effective treatment modalities targeting the pathology of AD remain to be resolved and revisited. Thus, regardless of the broad and dynamic studies, inspecting the mechanisms culpable for different pathologies is required

due to the significant gap in awareness of AD pathology [37]. The first pathology, as discussed previously based on the Aβ plaques, may accumulate for up to or more than 10 years without any signs/symptoms of AD before its precise diagnosis [38, 39]. NFTs hypothesis reviewed already explains, the total load of the tangles is associated with the decline of cognition in AD. Anyhow, the presence of NFTs is detected before the initiation of AD symptoms in both preclinical studies and non-symptomatic AD cases [40-42].

3.3. Role of Inflammatory Responses

In the past ten years, a third basic pathological element of AD has appeared that may be fruitful in understanding the pathogenesis of AD and is also associated with the above two basic pathologies. Studies have demonstrated that in AD patient's brain, not only Aβ plaques and NFTs are found, but there is also a constant inflammation led presence of inflammatory cytokines, such as Interleukin-6 (IL-6), Interleukin-1β (IL-1β), and Tumour necrosis factor-α (TNF-α) [43-45]. Various studies have emerged to investigate the inflammatory response in post-mortem tissues of AD patients and are now regularly looked at in AD-related preclinical studies [46, 47].

Anti-inflammatory cytokines (IL-4, IL-10, and IL-13) can activate M2 subtype microglia cells, surrounding amyloid neuritic plaques and can also regulate Aβ-induced production of the inflammatory cytokines. Recent data states that the level of pro-inflammatory cytokines remains increased in AD brains. IL-1, IL-10, and IL-13, along with TNF-α is a potent inflammatory cytokine that promotes the pathophysiological process and triggers signaling pathways that can regulate various cellular mechanism linked with gene expression, cell viability, synaptic integrity, and ion homeostasis [6].

Defense mechanism against toxins, infection, and injury is well understood in case of acute inflammation in the brain. However, any imbalance between pro-inflammatory and anti-inflammatory responses leads to chronic inflammation, which then further activates microglial cells and releases cytokines [48-51]. Microglia are the inhabitants of immune cells inside the CNS [52]. Microglial cells remain dormant, a 'relaxing' state in healthy brains, and are identified as branched cells with small somas [53, 54]. In this form, these cell somas remain static. However, these soma cells prepare themselves to expand and retract, inspecting their surroundings and linking with astrocytes and neurons [55-57]. They serve as the first line of defense systems whenever there is a threat of pathogens or injury to the brain. Microglia get activated in neurodegenerative diseases, tumors, and stroke, and these cells encircle dead or damaged cells and make area free from cellular debris, a phenotype known as phagocytic macrophages [58]. In AD, it is predicted that the existence of Aβ results in the activation of microglial cells and these microglia then move towards plaques and phagocytose the Aβ [59-61]. The constant activation/reactivation leads to a decline in the microglial binding and Aβ phagocytosing activity. In the milieu, the degradation of microglia leading enzyme activity conclusively reduces the breakdown of Aβ plaques [62, 63]. Apart from the microglia, astrocytes are also considered as one of the most important members for the degradation and clearance of Aβ. This serves as a trophic aid to neurons and maintains the protective boundary between neurons and amyloid deposits [64, 65]. In AD, the existence of large numbers of astrocytes correlated with Aβ deposits if these would produce certain molecules that help in the recruitment of astrocytes. However, it is evidenced that engaged astrocytes gather at Aβ plaque vicinity, leading to neuroinflammation and subsequent neurotoxicity induced by NO in the presence of L-arginine delivering enzyme argininosuccinate synthetase and inducible nitric oxide synthase (iNOS) [66]. Another report proposed that astrocytes may be responsible as an origin of Aβ because they reveal an excessive amount of β-site APP cleaving enzyme 1 (BACE1) as feedback to chronic stress [65].

4. 5-LIPOXYGENASE AND INFLAMMATION

5-LO is a monomer protein comprising of 673 amino acids and has been identified in various distinct mammalian species. Lipoxygenases (LO) are a cluster of iron-enclosed dioxygenases that catalyse oxidation reaction and add oxygen to AA, docosahexaenoic acid (DHA), and various polyunsaturated fatty acids (PUFA). LO enzymes are found in different isoforms depending upon the tissue type and their location, like epidermis type (LOX-3) or reticulocyte type (LOX-15). Some LO enzymes catalyze few reactions, such as the addition of molecular oxygen to AA at carbon 5, 12 and 15 in different ratios in reticulocytes. This results in the production of 5-, 12-, 15- hydroperoxy- eicosatetraenoic acid (HPETE) as an end product [67, 68]. Overall, there are five isoforms of LOs that are expressed in humans/animals: 15-LO, 12-LO, 3-LO, 8-LO, and 5-LO. This naming of the LOs is based on the position of oxygen added into substrate like AA [69]. These lipid mediators play an important role in the oxidative degradation of lipids, converting it into the peroxide as they exist in animals as well as in vegetal kingdoms [70, 71]. Among all the LOX enzymes, 5-LO is crucial which helps in the conversion of AA to 5(S)-HPETE and leukotrienes (LTs). Inflammatory mediators like LTs and inflammatory eicosanoids act on different receptors and persuade various responses like leukocytes chemotaxis and enhanced vascular permeability as well as several effects in neurons that are even not well known [72-74]. The LTs that remain present in the brain play a significant role in pathological alterations in brain tissues [75, 76]. However, lag time is required for the LO enzymes to activate the inactive ferrous form of the enzyme to the active ferric form. Even though the analytical performance of the LOs is still argumentative, its radical character is generally determined. Three stages are involved in sequence: (1) abstraction of stereo-selective hydrogen from a two allelic methylene group, (2) rearrangement of radicals, and (3) stereo-specific infusion of the oxygen molecule and decline of hydroperoxy-radical intermediate to the analogous anion [68].

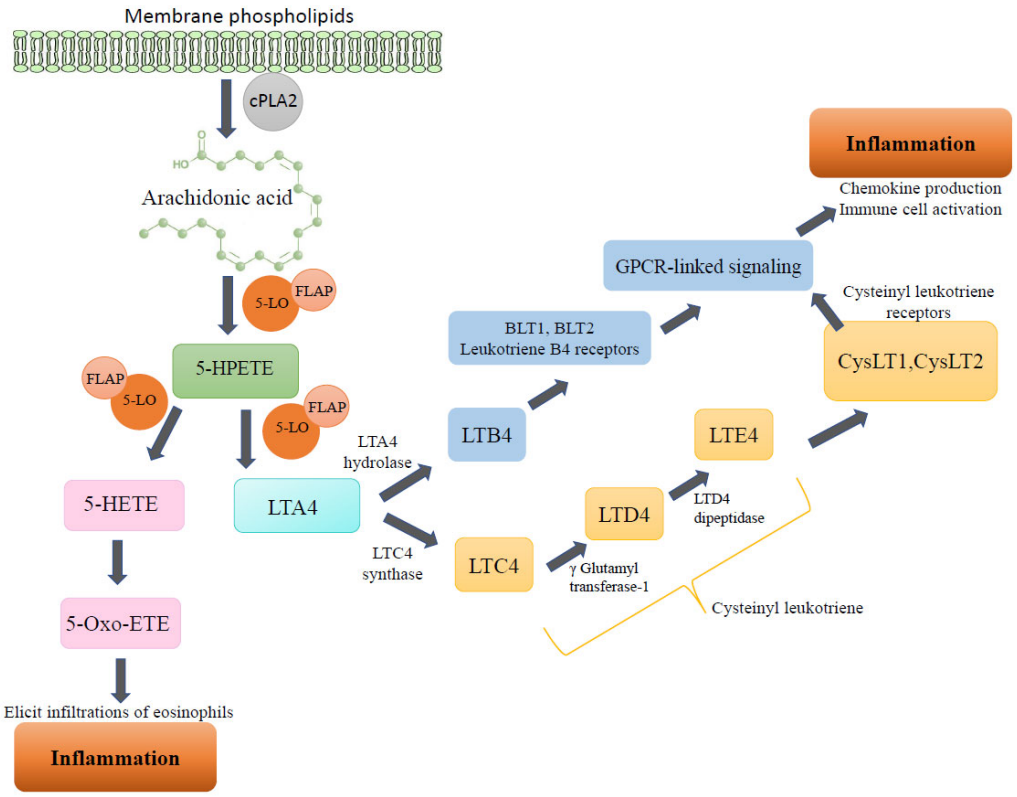

Fig. (2). Role of 5-Lipoxygenase enzyme (5-LO) in inflammation- Arachidonic acid is the primary substrate which is produced by metabolism of cytosolic phospholipase A2 (cPLA2). 5-LO acts on arachidonic acid to releases 5 HPETE which metabolizes to form Leukotrienes (LTA4) and 5-HETE. Furthermore, this leukotriene act on hydrolase and synthase to produce other leukotrienes (LTB4, LTC4). LTB4 bind to their respective receptors which are G-Protein coupled receptors and contributes in inflammation. Leukotrienes LTC4 by incorporating γ Glutamyl transferase-1 pursue to form LTD4 which act on LTD4 dipeptidase to generate LTE4. These leukotrienes collectively called as cysteinyl leukotrienes they bind to their receptors (CysLT1, CysLT2) which are again GPCRs and assist in Chemokine production, Immune cell activation and Inflammation. Whereas, 5-HETE which is produced from 5-HPETE in the presence of 5-LO binds to eicosanoid receptors to trigger inflammation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5. 5-LIPOXYGENASE AND CATALYTIC PATHWAYS

Figure **2** illustrates the role of 5-LO and its related catalytic pathways involved in the inflammation. AA is one of the main free fatty acids (FFA) produced by the metabolism of cytosolic phospholipase A2 ($cPLA_2$). In the initial two steps of biosynthesis, AA is oxidized at Carbon-5 to produce 5-HPETE in the presence of FLAP and 5-LO pursued by successive dehydration of hydroperoxide, yielding to an intermediate product LeukotrieneA_4 (LTA_4) and 5-HETE. Relying on the accessible enzymes, the extremely unsteady epoxide LTA_4 either hydrolyzed to LeukotrieneB_4 (LTB_4) in the presence of LTA_4 hydrolase or get associated to glutathione to produce LeukotrieneC_4 (LTC_4) with the help of LTC_4 synthase. The compound LTC_4 is further metabolized to LeukotrieneD_4 (LTD_4) and LeukotrieneE_4 (LTE_4) after successful termination of glycine and glutamic acid by glutamyl transferase and LTD_4 dipeptidase [77, 78]. LTB_4 receptors include Leukotriene B4 receptor 1 (BLT1) and Leukotriene B4 receptor 2 (BLT2), Cysteinyl leukotriene receptor 1 (CysLT1), and Cysteinyl leukotriene receptor 2 (CysLT2), which are G-protein coupled receptors and contribute to inflammation [79].

On the other hand, inflammatory mediators that are produced by the 5-LO act on the Oxoeicosanoid receptors. This includes eicosanoids 5-HETE and 5-Oxo-eicosatetraenoic acid (5-oxo-ETE). The metabolites of 5LO activation produce LTs and 5HETE that trigger chemotaxis of immune cell and are known to be a key player in the pathophysiology of inflammation in different diseases like asthma and allergy [80]. Importantly, the expression of 5LO and its metabolic products increase with an increase in the age of both animals and humans. The most vulnerable areas like the cortex and hippocampus are specifically sensitive to neurodegeneration and are usually found to be rich in 5LO protein levels in AD [81, 82]. There are numerous elements required by 5LO to become effective and concurrent to upsurge cellular calcium ions that motivate the transfer of the enzyme to the membrane from the cytosol. 5LO, in the membrane, is combined

with the integral membrane protein, which is commonly known as FLAP [83, 84]. Apart from oxidation, 5-LO and its activating protein FLAP play a major role in initiating inflammation in AD. Interruption in these pathways lowers the microglia as well as astrocytes in the animals with AD, as evident by the immunohistochemical analyses [85]. In addition, there is a correlated reduction in the levels of pro-inflammatory cytokines with the disruption in 5-LO or FLAP. In the brain ischemia-reperfusion model, it was reported that the translocation of neuronal 5-LO from the cytosol to the membrane was followed by the enhanced formation of LTs [86]. Therefore, inhibition of 5-LO reduces neurodegeneration in the ischemic brain [87].

6. 5-LIPOXYGENASE AND ALZHEIMER'S DISEASE

Various studies strengthen the involvement of 5-LO enzymes in the development of AD. This involves a comparison between the post-mortem studies of healthy control and AD brains and demonstrated that the levels of 5-LO were higher in the hippocampus and cortex regions of AD patient's brain. However, no significant change was observed when the assay was carried out between the cerebellum (a region lacking AD pathology) of both the brains of healthy control and AD [88, 89]. A genetic study conducted on humans revealed that 5-LO gene polymorphism is linked to early and late development of AD. However, large-scale populace studies are yet to affirm these findings. A separate study examined the epigenetic flaw of 5-LO in mononuclear peripheral blood cells of individuals with late development of AD and age-balanced controls. This demonstrated a remarkable increase in the expression of the 5-LO gene in AD patients as compared to the control ones [90-93].

The small protein FLAP triggers the 5-LO enzyme, leading to a complex formation, which conveniently produces 5-HPETE from AA that gets converted to LTs. FLAP remains on the nuclear membrane to behave as a conveyor of LOs [94]. It seems that both 5-LO and FLAP show a reduction in the fundamental pathology of AD. At the same time, they reduce the oxidative stress and inflammation induced by AD pathology. The inhibition of the 5-LO pathway in cultured hippocampal neurons of the rat demonstrated the decrease in reactive oxygen species (ROS) formation, induced by antibodies and successive calcium dysregulation in the concentration-controlled process [95]. Interruption in the 5-LO pathway prevented from glutamate-induced excitation toxicity in rats, particularly in older animals [96]. *in vitro* studies evidenced that *over*-expression of 5-LO does not result in oxidative stress itself, but when *over*-expressed in the presence of Aβ peptides, it lowers the levels of glutathione peroxidase and catalase enzymes [97]. This was observed that the inhibition in the pathway of 5-LO by a target inhibitor, pyrazole CNB-00, prevents the endoplasmic reticulum (ER) abnormality and toxicity of proteasome, promoted by Aβ peptide present in cultured neurons and *in-vivo* study [98]. Surprisingly, in *in-vitro* studies, blockage in FLAP is insufficient to shield against oxidative toxicity induced by the peptide Aβ. Evidences suggest that even after the decoupling of 5-LO from Aβ peptide metabolism, its capability to introduce molecular oxygen remains protected and preventing pro-oxidative characteristics in a LTs independent manner. However, the fact is not well understood, and therefore, more research must be carried out to investigate this phenomenon further. Moreover, inhibition of LTs is associated with preventing cognitive loss provoked by traumatic injury of the brain in rats due to the genesis of oxidative stress that is a well-established risk element for AD [99]. FLAP protein targeted drugs have already been used in humans. The agent, DG-031reduces the risk of myocardial infarction by lowering the release of LTB_4 [100]. An arthritis model showed that the mice lacking arachidonate 5-lipoxygenase activating protein (ALOX5ap), a protein-coding gene, does not initiate antibody accumulation against collagen. Thus, it represents that 5-LO controls inflammation without disturbing immune response [101]. Mice lacking ALOXap shows recovered AD like symptoms [102, 103]. Above evidences indicated that FLAP and 5-LO are together involved in the LTs pathway in neurological disorders.

LO is not only responsible for the synthesis of active lipids but also plays an essential role in oxidizing the lipid segments in the cell membrane. It produces the activators, causing structural changes and leading to maturation and differentiation of a variety of cells [104]. The mouse has a total of seven different Los and among these, five different LO has also been found in humans. This includes 5-LO, 12-LO (platelet-type and leucocyte-type), and 15-LO, which is divided into subtypes 15-LO-1 (leucocyte-type) and 15-LO-2 (epidermis type) [105, 106].

There are various tissues in which LOs are expressed and involved in different diseases like diabetes (both type1 and type 2), kidney diseases, atherosclerosis, and obesity [107, 108]. Currently, LOs are expected to play a key role in the development of neuronal diseases, including AD [90].

Arachidonate 5-Lipoxygenase (ALOX5) has also shown to play a prominent role in mediating inflammation in the brain. Cannabinoid Receptor 2 activation down-regulates 5-lipoxygenase (Alox5) expression by suppressing the JNK/c-Jun activation [109, 110].

Besides asthma and inflammatory reactions, the role of 5-LO in the induction or progression of AD is well evident. In AD, ALOX5 is overexpressed and its importance in neurodegenerative diseases needs to be discussed at least in brief [111]. Current research states that ALOX5 lacking mice show defensive action against anxiety, which may be due to the modification in neuronal function by ALOX5 [112]. Consecutive research was performed on a transgenic mouse model of AD, which described the efficacy of 5-LO inhibitor (Zileuton) and predicted that ALOX5 is either involved in the initiation or progression of AD [113].

To understand the role of LOs profoundly, a study in 2004 expressed the very first data that exposed the modified role of 12-LO in AD using post-mortem autopsy brain analysis [114]. The study highlights that levels of 12/15-LO protein are increased in the temporal and frontal cortex. This rise is a specific hallmark of oxidative degradation of lipids,

isoprostane 8, 12-iso-iPF2aVI, is and conversely associated with the amount of vitamin E, indicating a notable aspect of 12/15-LO acting as an oxidative stressor. Subsequently, the excitement of 12/15-LO leads to the excess production of 12/15-HETE in these cortexes, which are parallel with lipid peroxidation along with the observation of microtubule-associated protein tau (MAPT) protein in the cerebrospinal fluid of patients with AD [115].

Furthermore, the elevated levels of 12/15-HETE were also observed in the cerebrospinal fluid of the people with mild cognitive defects, stating that 12/15-LO performs a critical role during the progression and in the initial phase of AD. In an agreement, the lack of 12/15-LO reduces oxidative stress in the brains of mice deficient with apolipoprotein E (ApoE) [116].

7. CURRENT STATUS OF 5 LIPOXYGENASE IN ALZHEIMER'S DISEASE

The epidemiological study indicated that patients with AD would be a future burden and an enormous national health threat. In approaching the national health challenge of AD, currently, narrow options of AD therapy are available. However, few medications were made available to the public after phase II and phase III trials that either inhibit the enzyme acetylcholinesterase or target N-methyl D-aspartate (NMDA). But, most of these drugs are used for symptomatic treatment and are not a promising regimen in the treatment of AD as their fate is not clear [4, 7]. AD is considered a burden worldwide and there is a shortage of adequate therapeutic agents, therefore, target-oriented research that effectively acts on AD pathophysiology needs to be prioritized to settle this malady. Many studies have been performed to reveal the role of LO inhibitors in AD [117, 118]. Selective inhibition is found to be challenging because of the existence of many isoforms, and this narrows the successful development of therapeutic agents. Clinically approved drug-like zileuton is an anti-asthmatic drug which inhibits 5-LO. The research has been conducted targeting FLAP for making changes in 5-LO in pathophysiological surroundings. Fiboflapon is another clinically approved FLAP inhibitor that limits LTB_4 production and other LTs [119]. The curative effects of another drug (NCT01147744) have been confirmed in adults and juveniles with stubborn asthma [120]. Other FLAP inhibitors like quiflapon (MK- 591), veliflapon (DG-031), AZD6642, BRP-7, and BRP-187 are in clinical trials. The only FLAP inhibitor, which successfully finished phase II clinical trials in asthma, to date, is GSK2190918 [121]. Apart from targeting the 5-LO and FLAP, there is another study that focuses on NACHT (NTPase domain), LRR (Leucine-rich repeat), and PYD (Pyrin) domains containing protein 3, collectively called as cryopyrin. They remain encoded by the gene NLRP3 (nucleotide-binding domain like receptor protein 3). Till now, the discussion has been made on the role played by Aβ activation that is directly responsible for the progression of AD. But different studies state that Aβ ameliorates AD indirectly by activating NLRP3 inflammasome, which carries NLRP3, caspase-1, and ASC (Apoptosis-associated speck like protein containing a caspase). In the Aβ plaques of AD models of mice and also in AD patients, levels of the cleaved and activated caspase-1 were found to be elevated [122, 123]. As intracellular deposition of tau is not a ruling signature of diagnosis, tauopathy is also considered to be secondary in terms of AD. Fundamental tauopathy, like frontotemporal dementia (FTD), also shows cognitive defects along with neuroinflammation [124].

8. FUTURE POSSIBILITIES IN ALZHEIMER'S DISEASE

AD is one of the age-related progressive brain illnesses among the elderly population. The aforementioned report enlightened the role of inflammation played in the progression of AD, apart from Aβ and tau involvement and also highlighted the other elements that contribute to AD pathology. It is evident through literature that LO plays an important role in AD pathogenesis. Therefore, target-oriented investigation is the need of the hour. Although there are marketed preparations available for the inhibition of LO enzymes, natural compounds need more attention for therapy development. The diagnosis of AD is also insufficient and needs to be addressed to develop biomarker kits that will detect the early onset of AD. Usually, at the time of diagnosis of AD, the disease progression to advanced stage is always a concern. There is a need to investigate prognostic biomarkers of inflammation that will help the researchers in predicting the disease before it starts which is a greater challenge. Additionally, large scale investigation is required in AD patients and preclinical animal models to further explore the microglial signaling pathway and NLRP3 inflammasome activation.

CONCLUSION

In the last decade, understanding of various pathological changes in AD has been greatly expanded. However, target-based treatment is still lacking and needs to be discussed thoroughly. The pathological alterations in the brain due to AD include neurodegeneration, extracellular accumulation of Aβ plaques, and formation of intracellular NFTs of hyperphosphorylated protein Tau. The alteration of homeostasis between inflammatory (IL-1, IL-10, IL-13 and TNF-α) and anti-inflammatory cytokines (IL-4, IL-10, and IL-13) promotes the pathophysiological damages and further triggers different signaling pathways that can regulate other cellular mechanisms linked with gene expression, cell viability, synaptic integrity, and ion homeostasis. Along with this, microglia (a glial cell type), that remain present in the brain and spinal cord, act as primary resident immune cell. Inflammatory responses due to neurodegeneration further activate these microglia and clear the debris, including Aβ, by phagocytosis. Also, astrocytes gather at the surroundings of Aβ and further produce neuroinflammation and related toxicity.

Importantly, with these pathological changes, 5-LO mediated neuroinflammation is a major area of concern in the development of AD. FLAP is the small protein that triggers the 5-LO enzyme that produces HPETE and LTs from AA. Recent evidence undoubtedly suggests that the involvement of 5-LO promotes both the initiation and progression of dis-

ease in elderly age. In addition, different eicosanoids like LTs are generated by AA metabolism mediated by 5-LO and act as inflammatory mediators. This initiates chemotaxis and enhances vascular permeability in the neuronal cells. The increased expression of 5-LO and its related metabolic products with age are well evident. In a similar context, the interruption of 5-LO mediated pathways reduces the number of microglia as well as astrocytes, indicating reduced neuroinflammation.

Based on these opportunities, many studies have been conducted to develop 5-LO inhibitors in AD. However, selective inhibition is an area of great concern due to the presence of many isoforms of lipoxygenase. Undoubtedly, we need to explore all the different corners of 5-LO targeted investigation to add a milestone in the treatment of AD.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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