



5-lipoxygenase: Emerging Therapeutic Targets in Central Nervous System Disorders

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Abstract

5-lipoxygenase is an iron-containing a cytosolic enzyme that is responsible for the play of inflammatory leukotriene. Although they are generally known for their role in allergic asthma, allergic rhinitis, and others latest advances in the field of biomedical research, the part of this inflammatory mediator in a more extensive scope of illnesses, for example, in the inflammation-related with the central nervous system (CNS) disorder, vascular aggravation (atherosclerotic), and other disease. Expanded exercises of lipoxygenases, under obsessive circumstances, for example, ischemia, epilepsy, Alzheimer's illness, Parkinson disorder create neuroinflammation. The enzyme systems lipoxygenases that form hydroxy subsidiaries and leukotrienes utilize arachidonic acid after its discharge from neuronal membrane phospholipids by the activity of phospholipase A2.

However, significantly a more remains elusive as the research in this field is emerging and just a little has been found. In this review, we initially gave a general up to date data on the combination pathway and the receptors for the enzyme. Here, we survey learning of the elements of lipoxygenases in the brain and their relationship with neurodegenerative illnesses. Next, we summarized the present discoveries on their role in the brain disorders, with an understanding given to the future points of view.

Keywords: Neuroinflammation, Cerebral ischemia, Alzheimer's diseases, Zileuton, Cognitive deficit.

Introduction

The significance of the lipid inflammatory mediators in well-being and ailments has been raising the area of interest. Any of a class of a compound (as the prostaglandins, lipoxins, leukotrienes and thromboxanes) derived from straight-chain unsaturated fats (PUFAs/ polyunsaturated fatty acids) of twenty carbon units long chain that are processed or typically metabolized over to oxygen-containing product (such as arachidonic acid) and involve in cellular action called as the eicosanoids [1]. Arachidonate 5-lipoxygenase also known as ALOX5, 5-lipoxygenase, 5-LOX. 5-LOX is a non-heme iron-containing catalyst enzyme (EC one.13.11.34) that in human is encoded by the ALOX5 gene [2]. Leukotrienes (LTs) inflammatory mediators cause vascular permeability and phagocyte chemotaxis [3]. In leukotriene synthesis catalyst enzyme 5-lipoxygenase (5-LO) catalyzes the conversion of arachidonic acid to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and subsequently unstable intermediate leukotriene A4 (LTA4). This product would then be able to be metabolized into leukotriene B4 (LTB4), or conjugated with glutathione to form LTC4, LTD4, also known as cysteinyl leukotrienes generally [4]. 5-LOX is circulated within the cytoplasm, nucleus, or each in resting cells relying upon the cell type [5] [6].

Leukotrienes are lipid mediator of inflammation that binding to the specific G-protein coupled receptors on different target cells brings out their pro-inflammatory activities, which include attachment of leukocytes to vascular endothelium, chemotaxis of leukocytes, and recruitment of cytotoxic T lymphocytes at the site of inflammation [7].

One of six human lipoxygenases, 5-LO is expressed basically in numerous leukocytes: polymorphonuclear leukocytes (neutrophils and eosinophils), mast cells, B lymphocytes, monocytes/macrophages, nerve fiber cells, and foam cells of the human atherosclerotic tissue. LTA4 is converted by LTA4 hydrolase to the dihydroxy acid LTB4, and by LTC4 synthases to the glutathione conjugate LTC4. Other cysteinyl-LTs are formed by hydrolytic removal of g-Glu and Gly from LTC4 (yielding LTD4 and LTE4). In proinflammatory's background, LTs ordinarily stimulate a cellular response, that is the fastest onset and of Shorty duration (as phagocyte chemotaxis, increased vascular permeability, smooth muscle contraction). These are mediated by suggests that of

G-protein coupled receptors, BLT1/2 for LTB4 and CysLT1/2 and GPR17 for the cys-LTs. Anti-leukotrienes (CysLT1 receptor antagonist) are mainly used for the purpose of respiratory disease treatment basically asthmatic patient [8] [9]. Elucidation of the chemical structure of the 5-lox and their relationship with inflammation, their role has been primarily examined the pathophysiology of the asthmatic disease. Notwithstanding, in more recent days their role in numerous disease has been emerging and pathophysiological role of the lipid mediators in disease, such as cardiovascular diseases including with vascular inflammation and arteriosclerosis [10], cancer and CNS diseases (discuss in the next part of this review) shown. Herein, a summary has been made on the research findings on 5-LOX enzyme in different CNS diseases and the underlying mechanism by which they might be playing a crucial role in such mediation of the CNS diseases.

5-LOX : Key enzyme in Leucotriene biosynthesis

LTs are lipid messengers that assume central part of the immune response and tissue homeostasis [7]. Biosynthesis of LTs from AA was at first described in polymorphonuclear leukocytes and monocytes. First described in 1937 as the moderate responding substances of hypersensitivity (anaphylaxis) (SRS-A), these lipid mediators are currently known as the cysteinyl LTs (CysLTs), LTC4, LTD4 and LTE4[11]. Synthesis of LTs can be separated in two pathways: one to make CysLTs and another to make LTB4. 5-LO is the key protein in LT biosynthesis and is situated in the nucleus in some cell types and in the cytosol of others[12]. 5-LO is a 72-to 80-kd monomeric soluble protein containing one nonheme iron important for catalysis [13], osteosarcoma cell lines[14]. In this framework, expression of 5-LOX alone results about no recognizable cell 5-LO action following challenge with calcium ionophore A-23187. LT synthesis is just an occurred when these cells were expressed by 5-LOX & FLAP. T cells are expressed by FLAP [15], macrophages, and DC[16], but not on erythrocytes or endothelial cells. Cells were activated by immune complexes, bacterial peptides, and other stimuli elicit evoke an arrangement of occasions that incorporate cytosolic phospholipase A2 (cPLA2) and 5-LO translocation to the nuclear envelope to produce 5-hydroperoxy eicosatetraenoic acid (5-HPETE) from Arachidonic acid. Therefore, 5-HPETE is dehydrated to yield the epoxide LTA4, a significantly pivotal intermediate in the biosynthesis of inflammation and anaphylactic mediator. LTA4 undergoes transformation one of three possible fates relying upon

the cell context: hydrolysis, conjugation with glutathione, or transcellular metabolism to create bioactive lipid mediator [17]. In neutrophils and monocytes, LTA4 is converted over predominately to the chemoattractant LTB4 by LTA4 hydrolase [18], however, in human eosinophils, mast cells, and basophils, LTA4 is conjugated with decreased glutathione by LTC4 synthases to frame the first of the CysLTs, LTC4 [19]. After carrier-mediated cellular export, sequential cleavage of the glutathionyl side chain of LTC4 produces the extracellular metabolites

LTD4 and LTE4. LTB4 might be degraded by microsomal ω -oxidation and peroxisomal ω -oxidation in myeloid cells and hepatocytes. Degraded is accompanied by loss of biological activities. It is vital to take note that degradative enzymes are increased by the transcription factor peroxisome proliferator-activated receptor (PPAR) and this nuclear hormone receptor is thus initiated by binding with LTB4 [20]. This criticism circle confines the term of activity of LTB4.

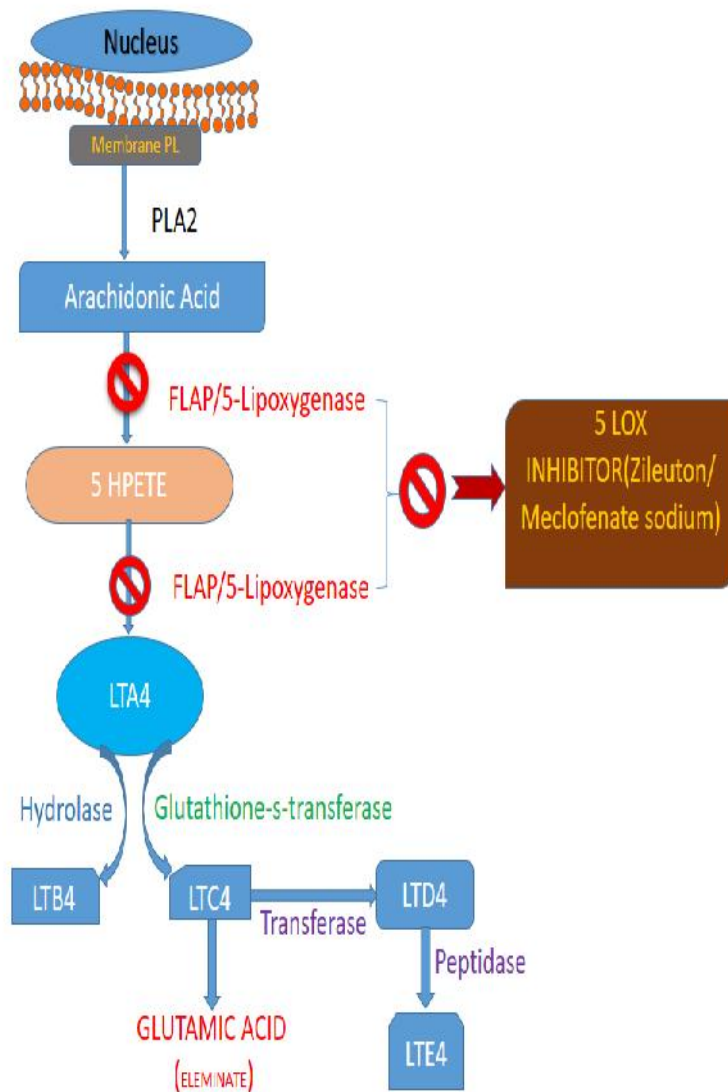


Figure 1

Role of 5-LOX in pathways of LT biosynthesis. Arachidonic acid is converted from membrane phospholipids by the activity of cytosolic phospholipase A2 (cPLA2) and conferred to a 5-LO chemical by FLAP. 5-LO compound converts arachidonic acid to an unstable intermediate named 5-hydroperoxyeicosatetraenoic acid (5-HPETE). Along these lines, 5-HPETE is dehydrated to yield the epoxide LTA4, a crucial transitional in the biosynthesis of inflammation. Enzymatic hydrolysis of LTA4 by LTA4 hydrolase brings regarding the arrangement of LTB4. On the opposite hand, LTC4 synthase catalyzes the conjugation of LTA4 with glutathione to LTC4, which might be converted to LTD4 and LTE4 by the activities of the transferase and peptidase proteins, individually.

5-LOX in CNS Diseases:

However, insufficient information is available on the extent to which 5-LOX-related drugs cross the blood-brain barrier. In spite of the fact that 5-LOX is basically known focuses in asthma and other hypersensitive disorders(allergic rhinitis/ urticaria), their role additionally has been appeared to be related with other human diseases, for example, in atherosclerosis, osteoarthritis, cancer and a few CNS diseases. Among research into CNS 5-LOX pathway indicates that 5-LOX may participate in a number of brain pathologies in the CNS diseases, they are related to brain injury like cerebral ischemia , Alzheimer's diseases, epilepsy, Parkinsons diseases.(figure-2)[21].

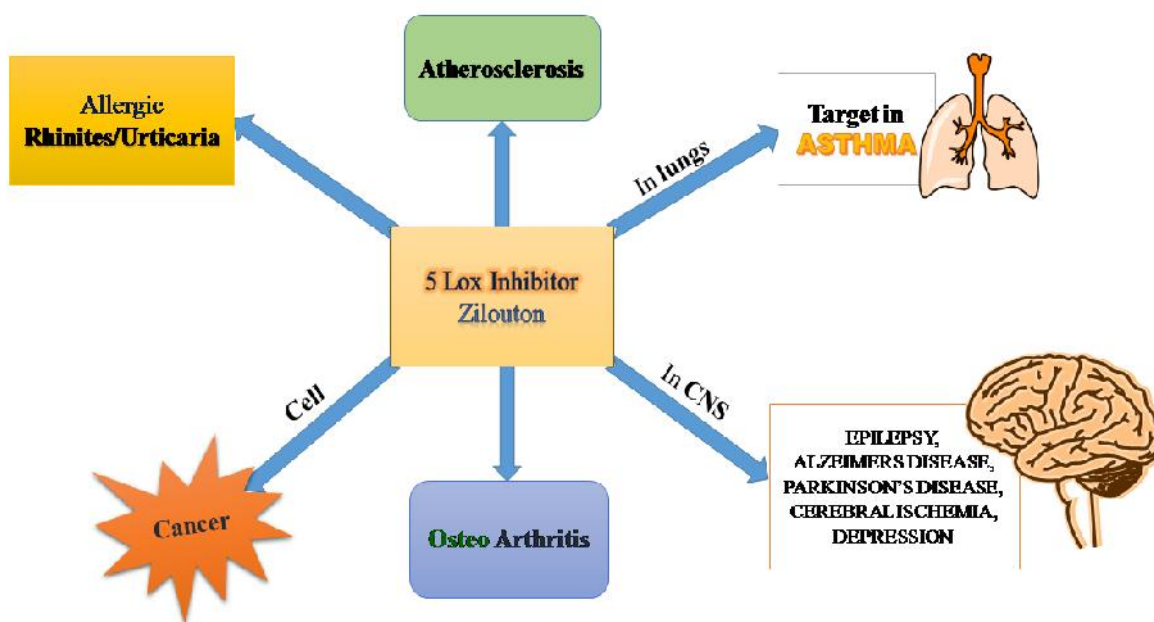


Figure-2

Parkinson's disease

The pathological signs of Parkinson's disease (PD) are the depletion of striatal dopamine caused by the degeneration of dopaminergic neurons in the substantia nigra (SN) located of the midbrain, the presence of cytoplasmic inclusions, known as Lewy bodies in the surviving neurons of SN, and the activation of glial cells. Current reports indicate that

brain inflammation and oxidative stress play a vital role in pathogenesis in this disease (Dauer and Przedborski, 2003; Gao et al., 2003; Ghosh et al., 2009) It has likewise been demonstrated that microglia and astroglia are activated in close proximity to the damaged or decaying on dopaminergic neurons in the SN (McGeer et al., 1988). Neuroinflammation is consequently an imperative component of neurodegenerative diseases

and variant inflammatory mediators contribute to the development of PD. *In vitro* study with rat mesencephalic neuroglia cultures, MK-886 likewise successfully protects dopaminergic neurons against MPP⁺ induce neuronal death. The 5-LOX result of 5-HETE is converted to LTA₄. Thus LTA₄ is enzymatically active compounds converted into different leukotrienes LTB₄. Leukotrienes are biologically active molecules that may sustain on messages by interacting with specific membrane G-protein coupled receptors and likely control transcription by binding an intranuclear orphan receptor. *In vitro* study found that LTB₄, but not LTD₄ or 5-HETE, increased the MPP⁺ induced cytotoxicity in the rat midbrain culture. Besides, MPP⁺ treatment enhanced the level of LTB₄ in the supernatant of cultures in a time-dependent way. Interestingly, *in vivo* animal experiment in mice demonstrated that MK-886 decreased the death of dopaminergic neurons in the substantia nigra and enhanced the dopamine, DOPAC, and HVA are concentrated in the striatum. Furthermore, the level of LTB₄ in the striatum and substantia nigra was additionally enhanced after MPTP challenge. LTB₄, a powerful chemotactic agent, amplifies the inflammatory response and increased the expression of IL-6, IL-12 and TNF alpha in the central nervous system.

We moreover understand that 5-LOX can be prompted in mice by MPTP infusion, and the 5-LOX inhibitor MK-886 diminished the death of dopaminergic neurons. MK-886 in like to reduce the LTB₄ articulation prompted by MPTP.

Epilepsy:

Status epilepticus (SE), a dangerous life-threatening condition, could be prolonged self-perpetuating seizure which needs prompt intervention to keep its damage and mortality.

Benzodiazepines, for example, diazepam and lorazepam, are suggested as the primary choice antiepileptic medicine to terminate seizure, nevertheless, if SE lasts more than 30-40 minutes, it seems to be more refractory to these agents[22, 23]. Therefore, applying fast treatments for treating SE, enhances neuroprotection and suppress the long-term equals such as epileptogenesis, neuronal damage and cognitive deficits[24].

Licofelone (A new generation substrate analogue of arachidonic acid, is a double competitive inhibitor of cyclooxygenases (COX-1 and COX-2) and 5-lipoxygenase (5-LOX) enzymes) applied anticonvulsive effects against SE induced by lithium-pilocarpine in male Wistar rats in a dosage-dependent way. Pre-treatment with the NO precursor L-arginine reduced the anticonvulsive effects of licofelone, though the non-selective NOS inhibitor L-NAME potentiated the protective effects of licofelone. 5-LOX is an enzyme that additions oxygen in arachidonic acid, convert to leukotrienes, which are potent mediators in inflammatory processes. LOX, for the most part, exists in brain tissue and neurons and may participate in neurodegeneration[25, 26]. 5-LOX is unregulated in different CNS disorders, such as multiple sclerosis, stroke, and Alzheimer's disease[27-29].subsequently, 5-LOX inhibitors have been thought to be neuroprotective. Furthermore, the end product of 5-LOX, leukotrienes, can induce NO synthesis [30], while it has been indicated for that NO donor compound, LOX inhibitor activity [31]. Many molecular signaling pathways are activated to provoke epileptogenesis. Among these proposed mechanisms, activation of the AMPA, kainite, and NMDA receptors have been reported to assume a key role in neuronal excitability in seizures[32]. iNOS inhibition could potentiate the anticonvulsive effects of the COX/5LOX inhibitor licofelone on SE induced by lithium-pilocarpine, neuronal damage because of seizures is related to upregulation of iNOS in the hippocampus[33]. utilizing licofelone and specific NOS inhibitors in a model of chemical-induced clonic seizure, we demonstrated the potential advantages of interactions of COX/LOX and iNOS/NO systems as an antiepileptic treatment.

Brain injury

Cerebral ischemia is one amongst the foremost inflammatory reaction cause of death and incapacity worldwide cause a serious clinical and socioeconomic effect. Though the pathophysiology of brain ischemia, the inflammatory process plays a critical role in pathogenesis, causative to the development of brain injury[34].The cerebral ischemia-induced inflammatory reaction, blood-brain barrier (BBB) disruption [35], and neuronal apoptosis [35], all of that increase the extension of neuronal disease and cerebral localized necrosis[36, 37]. Brain ischemia (cerebral ischemia, cerebrovascular ischemia) is a condition in which there is insufficient blood flow to the brain to fulfill metabolic demand [38]. This prompts poor

oxygen supply or cerebral hypoxia and therefore to the death of brain tissue [39]. Brain ischemia, the brain can't perform anaerobic metabolism because of the loss of oxygen and substrate. The brain can't an amendment to anaerobic metabolism and in energy store that it doesn't have any long-term levels of adenosine triphosphate (ATP) drop quickly and approach zero to within 4 minutes. Without biochemical energy, cells begin to lose the ability to maintain electrochemical gradients. Thus, there is a massive influx of calcium into the cytosol, a monstrous release of glutamate from synaptic vesicles, lipolysis, calpain activation, and the arrest of protein synthesis[40, 41].72 hours MCAO (Middle Cerebral Artery Occlusion) treated central cerebral ischemia rat model exhibited that 5-lox drugs zileuton was showed to attenuate cerebral infraction, neuronal damage, and neuronal apoptosis. Some examination showed that zileuton decreases the expression of caspase-1 mRNA in ischemic hemisphere, up-regulation of the expression of the procaspase-3 protein, and down-regulates the expression of the cleaved caspase-3 protein in ischemic hemisphere [42]. 5-LOX inhibitor zileuton inhibits neurological deficit scores, cerebral necrosis, and neuronal damage in ischemic rat brain, which demonstrates the neuroprotective effects of zileuton in cerebral ischemia. Semilogically, decreases neurological deficiency demonstrate that zileuton enhances neurological capacity in ischemic stroke. Pathologically, decreases cerebral infraction demonstrates that zileuton enhances cerebral bloodstream in ischemic stroke.Zileuton on caspase-1 and caspase-3 expression in rats of cerebral ischemia. As we know that, the caspase family has been separated into two main subfamilies, one involved with inflammation and one associated with apoptosis. A few caspases play a part in both inflammatory and apoptotic cascades, including caspase-1, caspase-11, and caspase-12 [43-45]. Caspase-1 plays an essential role in inflammatory reaction by handling pro IL-1 into the active cytokine develop IL-1 [46]

Zileuton inhibits the inflammatory reaction and the expression of IL-1 at any partly somewhat through the inhibition of caspase-1. As one of the caspases family, caspase-1 additionally plays a key role in apoptotic cell death, [43] provide direct evidence to demonstrate that caspase-1 is involved with ischemia-induced neuronal cell death. The key role of caspase-1 in zileuton's against apoptotic property.Caspase-3, the effectors of the apoptotic signaling pathway is expressed, activated, and cleaved in cerebral ischemia. Procaspase-3 and cleaved caspase-3, two different

types of caspase-3, were generally used to be a list of the presence of cell apoptosis. Procaspase-3, the pro form of caspase-3, would be reduced during the process of apoptotic cell death[47]. The expression change of procaspase-3 and cleaved caspase-3 after MCAO was turned around by the administration of zileuton, exhibiting that zileuton attenuates neuronal apoptosis possibly of caspase-1 and caspase-3 pathway. So we understand that zileuton provides a neuroprotection against ischemic stroke, and this neuroprotection might be associated with the inhibition of neuronal apoptosis and the molecular regulation of caspase-1, procaspase-3, and cleaved caspase-3 [48].

Alzheimer's disease

ALZHEIMER'S DISEASE (AD), the foremost well-known type of dementia in the elderly, is pathological neuropathy logically by extracellular saniles plaques consists of b-amyloid (Ab) plaques and intracellular neurofibrillary tangles (NFTs). These injuries are connected neuronal with loss of memory and oxidative awkwardness occurring in lipid peroxidation, DNA, and RNA damage, and neuronal degeneration. The incidence of the sporadic AD is to a largely characterized by oxidative stress (anxiety), neuroinflammation and an extraordinary load of proinflammatory cytokines, the 5-LOX pathway directs the proinflammatory mediator individual within the cerebral cortex [49]. COX/ 5-LOX are mediator individuals of such inflammatory related neurotoxicity [50] and licofelone, a unique novel double inhibitor of COX/5-LOX, reduces oxidative stress/anxiety and increased burden of proinflammatory cytokines in a rat model of sporadic AD [51, 52]. Mild cognitive impairment (MCI), which fills in as a prodrome to AD, is similarly associated with 5-LOX upregulation in the early development of the diseases [53]. Alzheimer's disease (AD) is a major cause of infirmity and fatality if not adequately treated [54] [55] [56].

5-LOX and FLAP have similar long been recognized to be related with various types of AD [57] [58] [59] [60] with a few components [61] [62] [63]. 5-LOX is elevated in AD brain and is immunoreactive which will be involved with post-translational alterations of the Ab saniles plaques and NFTs [64]. It is an endogenous modulator of Ab develop in vivo and takes part in corticosteroid-depended Ab propagation [65]. In line with the way that Ab aggregation is depended on 5-LOX, specialists as double inhibitors

of Ab and 5-LOX are created [66]. Pharmacological studies using zileuton additionally exist indicating the ameliorative impact of the medication on AD phenotypes in varied animal models [67] [68] [69]. Genetic knockout examination study on the 5-LOX gene has to prove beneficial effects against AD pathology supporting the pharmacological discoveries [65].

Conclusive remark and Future outlook

The inflammatory milieu relative to 5-LOX has been involved in a scope of pathological conditions, for example, in asthma, allergic rhinitis, cardiovascular disease, and neurological dysfunctions. Hypersensitive reactions are settled, and their pathophysiological part in the brain is very little known and significantly much more attention should be given to increase the most extreme comprehension of their role in CNS diseases.

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Conflict of interest

The authors declare no conflict of interest.

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