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12/15 Lipoxygenase as a Therapeutic Target in Brain Disorders

Beyin Hastalıklarında Tedavi Hedefi: 12/15 Lipoksijenaz

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ABSTRACT

Lipoxygenases are a family of lipid-oxidizing enzymes, which generate eicosanoids and related compounds from arachidonic acid and other polyunsaturated fatty acids. These metabolites play important roles in physiology and pathogenesis of host defense mechanisms, cardiovascular diseases, cancer, inflammatory, allergic and neurodegenerative diseases. The 12/15-lipoxygenase (LOX) is special in that it can directly oxidize lipid membranes containing polyunsaturated fatty acids, without the preceding action of a phospholipase, leading to the direct attack on membranous organelles, such as mitochondria. The cytotoxic activity of human 12/15-LOX is up-regulated in neurons and endothelial cells especially after a stroke and thought to contribute to both neuronal cell death and blood-brain barrier leakage. The discovery of inhibitors that selectively target recombinant 12/15-LOX *in vitro,* as well as possessing activity against the murine orthologous *ex vivo,* could potentially support a novel therapeutic strategy for the treatment of stroke and other brain disorders related to 12/15-LOX. Here we reviewed 12/15-LOX chemistry shortly, and the diseases in which 12/15-LOX has a role in their pathophysiology and recent advances of 12/15-LOX inhibitors as a treatment option for neurological diseases.

Keywords: Lipoxygenases, stroke, haemorrhagic transformation, 12/15-LOX inhibitors

ÖZ

Lipoksijenazlar, araşidonik asit ve diğer çoklu doymamış yağ asitlerinden eikosanoid ve ilgili bileşikleri üreten lipit oksitleyici enzim ailesindendir. Bu metabolitler konak savunma mekanizmaları, kardiyovasküler hastalıklar, kanser, inflamatuvar, alerjik ve nörodejeneratif hastalıklar gibi birçok hastalığın patogenezinde önemli rol oynar. 12/15-lipoksijenaz (LOX), bir fosfolipazın etkisine maruz kalmaksızın, çoklu doymamış yağ asitleri içeren lipit membranları doğrudan okside edebilmesi nedeniyle ve dolayısıyla mitokondri gibi membranöz organeller üzerinde doğrudan saldırıya yol açması bakımından özeldir. İnmeden sonra 12/15-LOX'un sitotoksik aktivitesi, nöronlarda ve endotel hücrelerinde artar ve hem nöronal hücre ölümüne hem de kan-beyin bariyeri sızıntısına katkıda bulunur. Seçici olarak rekombinant 12/15-LOX'u hedefleyen *in vitro* ve murin ortoloğuna karşı *ex vivo* geliştirilen inhibitörlerin keşfi, 12/15-LOX ile ilişkili inme ve diğer beyin hastalıklarının tedavisi için yeni bir terapötik stratejiyi gündeme getirmiştir. Bu derleme yazısında 12/15-LOX biyokimyasından kısaca bahsedildikten sonra, ardından 12/15-LOX'un patofizyolojisinde rol oynadığı hastalıklar ve 12/15-LOX inhibitörlerinin nörolojik hastalıklar için bir tedavi seçeneği olarak incelendiği son çalışmalar gözden geçirilmiştir.

Anahtar Kelimeler: Lipoksijenaz, inme, hemorajik transformasyon, 12/15-LOX inhibitörleri

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INTRODUCTION

Lipoxygenases (LOX) oxidase polyunsaturated fatty acids (PUFA), which produce fatty acid metabolites (1). These metabolites play important roles in physiology and pathogenesis of host defence mechanisms, cardiovascular diseases, cancer, inflammatory, allergic and neurodegenerative diseases.

Although mammalian lipoxygenases have been realized for 40 years, their physiological and pathophysiological actions are not completely elucidated. Here we focused on a short view of lipoxygenase biochemistry, then the contribution of 12/15-LOX in animal models of brain disorders and available human data, at the end as a treatment option of 12/15-LOX inhibitors in neurological diseases.

SUMMARY OF LIPOXYGENASE BIOCHEMISTRY

Lipoxygenases are involved in non-heme iron containing enzyme family which tightly regulated by membrane lipids, ATP, diacylglycerols, phosphatidylinositol products, phosphorylases, intracellular calcium levels, and numerous lipoxygenase related proteins (2). They are commonly expressed in higher plants and mammals (1, 2). The first LOX was found in dried soybean seeds six decades ago and the researchers tried to define the molecular aspects of the catalytic features of this enzyme. Firstly defined animal LOX was named as arachidonic acid 12-lipoxygenase (ALOX12), and found in human blood platelets in 1974 (3). After a short while, a new LOX-isoenzyme was announced in the immature rabbit red blood cells lysate (4). The dominant LOX-substrates are linoleic acid and arachidonic acid in mammalian cells. There are six different human LOX isoforms among them the best studied ones are possibly ALOX5 and ALOX15 (5, 6). Recently characterized LOX-isoforms are classified with their sequence resemblance to any of the human LOX-isoforms. This categorization model fits to most mammalian LOXs. There are six LOX genes (ALOX15, ALOX15B, ALOX12, ALOX12B, ALOXE3, ALOX5) in human genome whose expression leads to six functionally distinct

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LOX-isoforms. One of them is ALOX15 that oxygenates arachidonic acid, this reaction is specific to a mixture of 15S-HpETE (90%) and 12S-HpETE (10%) (1). ALOX15 was formerly named 12/15-LOX because of this dual reaction specificity. In contrast to the human genome, there are seven functional LOX genes in mouse genome (7).

The functional equivalent of human ALOX15 in mouse has been studied for several years. Of these studies genome sequence associations, localization of the chromosome and comparison of the enzyme features propose that the mouse leukocyte-type 12-LOX (previous nomenclature) and the human reticulocyte-type 12/15-LOX (previous nomenclature) are orthologous enzymes. Although the specificity of the reaction is different from arachidonic acid oxygenation, mouse Alox15 may constitute the functional equivalent of human ALOX15 as, enzyme orthologous meet similar functions in different organisms (1).

Lipoxygenase activity is responsible of free fatty acids mono-oxygenation, fatty acids double and triple oxygenation (lipoxin synthase reaction) and oxygenation of phospholipids, cholesterol ester, biomembranes and lipoproteins in the cell (8). In human thrombocyte 12 (S)-LOX is the main source of 12-HETE, which is a pro-inflammatory molecule and causes vasodilation, neutrophil chemotaxis, monocyte adhesion and cellular proliferation (9, 10).

12/15 LIPOXYGENASES IN BRAIN DISORDERS

The most studied brain disorder related to 12/15 lipoxygenase is rodent stroke models. Stroke is the leader disease of morbidity and the fifth reason of mortality in the United States (9). A human being dies of stroke every four minutes (9, 11). Economic burden of stroke with cardiovascular diseases is more than the other diseases including cancer. The yearly expense of stroke and other cardiovascular diseases is estimated as $316,6 billion in the United States (9). There are two types of stroke in which mostly seen one is ischemic stroke and it is about 85% of all stroke cases, the other one is haemorrhagic stroke representing nearly 15% of stroke patients. Although stroke has these disastrous results, tissue plasminogen activator (tPA) is the only FDA-approved treatment option for acute stroke. Actually tPA has numerous shortages that include the narrow therapeutic window, low number of cases getting this treatment, and life threating adverse reactions like haemorrhage (12–15). That is why tPA can not be administered for haemorrhagic strokes. Thus new treatment options alone or in combination with tPA are of great interest in stroke management.

After an ischemic stroke there is a core region of infarct where blood supply suddenly and massively drops which causes cellular death. This core region is surrounded by a salvageable tissue called penumbra, in which tissue blood supply is reduced and is at risk of death. From death tissue and depolarized neurons there is a huge amount of glutamate release which causes excitotoxicity and increase in permeability of blood brain barrier (16). Oxidative stress is another source of brain injury after stroke and 12/15-LOX (also known as 15-LOX-1 or leukocyte-type 12-LOX) is involved during these pathophysiological processes.

There is amount of data providing the importance of 12/15-LOX in ischemic stroke in the literature. Bazan group showed that there is an increased level of arachidonic acid in the brain following ischemia (17). Then two separate groups demonstrated that arachidonic acid injection into the brain can cause oedema (18, 19). Finally, the increase in lipoxygenase metabolites, including both 5-LOX derived leukotrienes and the 12/15-LOX metabolite 12-HETE, in the gerbil forebrain following ischemia was shown by Moskowitz and colleagues (20). After a while, the function of 12/15 LOX in cell death process triggered by oxidative stress in cultured neurons was presented to the literature (21). However, the specific involvement of 12/15-LOX in experimental stroke models in rodents was not elucidated till 2004 (22, 23). Most of cerebral ischemia studies with 12/15-LOX have been carried out in rodents. In mice, inducing an experimental stroke by filament model (transient MCAO), 12/15-LOX was found to be expressed in peri-infarct region of the cortex by immunohistochemistry (23). It was also shown that apoptosis-inducing factor (AIF) is increased in the same cells positive for 12/15-LOX and baicalein, a nonspecific 12/15-LOX inhibitor, decreased infarct volume (24). This data links 12/15-LOX to an apoptotic cell death mechanism. Importantly, 12/15-LOX is elevated both in neuronal and in endothelial cells, suggesting that this may lead to both neuron death and vascular injury (25).

The involvement of 12/15-LOX investigated not only in transient MCAO model but also in permanent cerebral ischemia model in mice (26). In a recent study, $FeCl_3$-induced persistent distal MCAO and $FeCl_3$-induced ischemia/recanalization with tPA model used in C57Bl6 and CD1 mice and increased immunoreactivity of 12/15-LOX was shown in peri-infarct regions (27).

The contribution of 12/15-LOX in brain injury following global ischemia was also investigated. Cardiac arrest has high death rate and major morbidity in long-term survivors because of global ischemia. van Leyen group used a mouse bilateral closure model of transient global ischemia that leads to widespread injury in cortex, striatum, and hippocampus in which 12/15-LOX was increased (28). However, there was a protection from global cerebral ischemia in 12/15-LOX knockout mice compared to wild-type ones and knockout mice had lower neurologic deficit (28). LOXBlock-1, lipoxygenase inhibitor, similarly decreased neuron death both in pre-injury administration, and in mice treated one hour after onset of ischemia (28).

Baicalein also inhibited 12/15-LOX and GSK3β action, decreased β-secretase enzyme (BACE1), reduced the total Aβ concentration, and stopped tau phosphorylation of APP/PS1 mice (29). This suggests the role of 12/15-LOX involvement in Alzheimer Disease models. Hence different models in different species were studied when investigating the contribution of 12/15-LOX in brain disorders.

Human Data Related to 12/15-Lipoxygenase Involvement in Brain Disorders

Human data related to 12/15-LOX involvement in brain disorders are limited in the literature. A study showed elevated cerebrospinal fluid (CSF) levels of 12-HETE in subarachnoid hemorrhage patients, and elevated levels of 12-HETE were also found in the CSF following traumatic brain injury (30, 31). Similar measurements in ischemic stroke patients have not been reported to date. However, Yigitkanli et al. showed increased 12/15-LOX in the peri-infarct cortex of two stroke patients, suggesting 12/15-LOX may contribute to stroke injury in humans, as well (32). In a study, the polymorphism of ALOX15 gene in ischemic stroke cases of northern Chinese Han population was investigated. According to this study, rs7217186 and rs2619112 polymorphisms of this gene were related to male ischemic stroke cases and in atherosclerosis related ischemic stroke patients (33).

Another data comes from human atherosclerotic plaque studies that found a meaningful elevation of 12/15-LOX expression in arteries including aortic, carotid and femoral (34–36). However, only few studies revealed a higher 12/15-LOX expression with lower lesion severity in clinical samples of human (37, 38). Especially, a C to T substitution at position-292 polymorphism in 12/15-LOX promoter was related to a decrease in atherosclerosis probability. This promoter region regulates its increased expression and activity (35, 36). In summary, several cell culture and animal model studies as well as human data have revealed that 12/15-LOX has a dual role for atherosclerosis (39).

12/15-LOX participation in the developing human brain was investigated in human paraffin-embedded tissue of periventricular leukomalacia obtained from 20 to 43 postconceptional weeks' cases by immunohistochemistry. The expression of 12/15-LOX was shown in macrophages of the focally necrotic lesions of the periventricular white matter, in glial cells of the surrounding white matter with reactive gliosis, in activated microglia that is CD68-positive and in premature and mature oligodendrocytes. This study shows the involvement of 12/15-LOX activity as an inflammatory mediator of damage in periventricular leukomalacia, and oligodendrocytes injury or death (40).

Another disease studied related to 12/15-LOX is Alzheimer's disease (AD). 12/15-LOX activity and protein levels were investigated in diverse brain areas of histopathologically definite AD patients and controls, because this enzyme is a major source of oxidative stress (41). Western blot analysis and immunohistochemical studies confirmed that the amount of 12/15 LOX was higher in affected frontal and temporal areas of AD brains compared to controls, while there was no difference in the cerebellum of two groups (41). There was an elevated levels of 12/15-LOX (12/15-hydroxyeicosatetraenoic acids) products in AD brains compared to controls (41). It was directly related to peroxidation of brain lipids, and inversely correlated with the levels of vitamin E. In addition, genetic deletion of 12/15-LOX resulted in a decrease of oxidative stress response of the cells following incubation with H_2O_2 or amyloid beta *in vitro*. Altogether these results demonstrate that the metabolic pathway of 12/15-LOX is elevated and associates with an oxidative discrepancy in the AD brain, suggesting the involvement of 12/15-LOX in the pathogenesis of this neurodegenerative disease (41).

12/15-LOX INHIBITORS

These *in vivo* and *in vitro* studies on human and animal models have caused the detection of numerous 12/15-LOX inhibitors. Many laboratories have discovered powerful and selective human 12/15-LOX inhibitors recently, but many of these inhibitors represent antioxidants, which reduce the active site iron of LOX including nor-dihydroguaiaretic acid, baicalein, tocotrienol, and curcumin (42–46). Some pharmaceutical companies have produced the most drug-like 12/15-LOX inhibitors prior to last investigations, that have low nanomolar potency (47). Though, these inhibitors had modest physical properties such as low solubility and Logp, they also had modest pharmacokinetic features for *in vivo* use. Besides, they were not assessed in parallel against mouse 12/15-LOX, so it is doubtful any one can be accepted as potential drug targets and would be useful in the rodent experiments. Selective inhibitors targeting recombinant human 12/15-LOX *in vitro*, and shown to be active against the murine orthologous *ex vivo*, can be regarded as a new treatment option for acute stroke, one of them is LOXBlock-1 that has effective in decreasing infarct size and limiting tPA bleeding side effect (32, 42, 48). Hence, the 12/15-LOX inhibitors can be used even in the ambulance as a first-line therapeutic option for acute stroke and may be combined with tPA to increase its safety. Besides, 12/15-LOX inhibitors may be a very useful option in anticoagulation related haemorrhagic transformation (HT) model. In a recent study, C57BL6J mice or 12/15-LOX knockout mice were anticoagulated with oral warfarin via drinking water then they were exposed to transient MCAO for 3 hours of severe ischemia or 2 of hours ischemia and tPA infusion, with or without the 12/15-LOX inhibitor, ML351 (49). In this study, warfarin treated groups developed reproducible elevated international normalized ratio levels and meaningful HT in both models. However, 12/15-LOX knockout mice displayed less HT following severe ischemia, and ML351 decreased HT in wild-type mice (49). ML351 still independently decreased haemorrhage after normalizing to infarct size. HT following tPA treatment was similarly reduced by ML351 (49).

Not only synthetic 12/15-LOX inhibitors but also endogenous substances, which act through of 12/15-LOX studied in stroke models. In a recent study, it was shown that the neuroprotective effect of taurine in an acute permanent middle cerebral artery occlusion model of rats may be due to the down-regulation of 12/15-LOX (50).

CONCLUSION

12/15-LOX has many effects in the pathogenesis of many diseases including cardiovascular diseases, cancer, inflammatory, allergic and neurodegenerative diseases. Selective inhibitors targeting recombinant human 12/15-LOX *in vitro* and *in vivo*, and shown to be active against the murine orthologous *ex vivo*, can be regarded as a new treatment option for acute stroke and other brain disorders related to 12/15-LOX. The 12/15-LOX inhibitors can be used even in the ambulance as a first-line therapeutic option for acute stroke and may be combined with tPA to increase its safety the only currently available acute ischemic stroke therapeutic. Besides 12/15-LOX inhibitors may be a very useful option in anticoagulation related haemorrhagic transformation. Clinical studies will elucidate the importance of 12/15-LOX inhibitors in neurological diseases.

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