Balkan Med J 2025;42:579-81

Lipoxin A4 (LXA4) as a Potential Drug for Autoimmune Uveitis

Undurti Narasimha Das

Department of Pharmacology, Atatürk University Faculty of Medicine, Erzurum, Türkiye
UND Life Sciences, WA, United States

Essential fatty acids (EFAs)-cis-linoleic acid (LA,18:2 n-6) and alpha-linolenic acid (ALA, 18:3 n-3)-are widely distributed in the diet and serve as precursors of several bioactive lipid molecules, including prostaglandins (PGs), leukotrienes (LTs), and thromboxanes (TXs), which exert predominantly pro-inflammatory effects. Both LA and ALA undergo enzymatic conversion by desaturases (Δ^6 and Δ^5) and elongases, giving rise to gamma-linolenic acid (GLA, 18:3 n-6), dihomo-GLA (DGLA, 20:3 n-6), and arachidonic acid (AA, 20:4 n-6) from LA and to eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3) from ALA. From AA, PGs and TXs of the 2-series and LTs of the 4-series are produced, whereas EPA gives rise to PGs and TXs of the 3-series and LTs of the 5-series, through the action of cyclooxygenase-2 (COX-2). Although all of these metabolites are pro-inflammatory, those derived from EPA are less so than those formed from AA. Importantly, AA is also the precursor of lipoxin A4 (LXA4), a potent anti-inflammatory molecule. Similarly, resolvins of the E-series are derived from EPA, while resolvins of the D-series, protectins, and maresins are generated from DHA; all of these have anti-inflammatory activity. Notably, DHA does not produce PGs, TXs, or LTs. Thus, AA, EPA, and DHA serve as precursors of both pro-inflammatory (except DHA) and anti-inflammatory eicosanoids (Figure 1). The balance between these metabolites is expected to determine the overall outcome of the inflammatory response.

LXA4, resolvins, protectins, and maresins exert their anti-inflammatory effects primarily by inhibiting the production of pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and macrophage migration inhibitory factor (MIF), while enhancing the formation of anti-inflammatory cytokines. They also suppress the expression of NF-κB, COX-2, and the cGAS-STING pathway. Interestingly, the fatty acids GLA, DGLA, AA, EPA, and DHA themselves also demonstrate anti-inflammatory activity to some extent, by reducing the expression of IL-6, TNF-α, NF-κB, and COX-2 (Figure 2). The significance of AA, EPA, and DHA lies in their role as integral components of the phospholipid fraction of all cell membranes. Various internal and external stimuli activate phospholipase A2 (PLA2), which in turn promotes the release of AA, EPA, and DHA-the precursors of multiple eicosanoids.

There is evidence that IL-6, TNF-α, MIF, PGs, LTs, and TXs are released by M1 macrophages, dendritic cells, NK cells, T cells, and other immunocytes, whereas M2 macrophages produce IL-10, LXA4, resolvins, protectins, and maresins. Pro-inflammatory cytokines activate PLA2, thereby promoting the formation of PGs, LTs, and TXs, while anti-inflammatory cytokines enhance the generation and release of LXA4, resolvins, protectins, and maresins. This process is reciprocal; for example, PGE2 stimulates the release of IL-6 and TNF-α, whereas LXA4 induces the production of the anti-inflammatory cytokine IL-10. This dynamic crosstalk among immunocytes, cytokines, and eicosanoids regulates the inflammatory process and immune response-both innate and adaptive-while promoting the resolution of inflammation, facilitating wound healing, and restoring homeostasis. Several aspects of the complex interactions among EFAs, eicosanoids, LXA4/resolvins/protectins/maresins, cytokines, macrophages, and T cells in the regulation of inflammation and immunity (Figure 2) have been discussed in detail elsewhere.[1-5] Collectively, these studies suggest that bioactive lipids may play a significant role in the pathobiology of uveitis.[1-6]

Lipoxins appear to regulate both innate and adaptive immune systems-including neutrophils, macrophages, and T and B cells-through their ability to modulate NF-κB, activator protein-1, nerve growth factor-regulated factor 1A binding protein 1, and peroxisome proliferator-activated receptor γ, thereby controlling the expression of numerous inflammatory genes.[1-6] In an animal model of lipopolysaccharide (LPS)-induced posterior uveitis, characterized by retinal neuroinflammation due to activation of resident microglia (astrocytes and Müller glia), lipoxins were shown to reduce retinal inflammation by inhibiting CXCL9 (MIG) and CXCL10 (IP-10).[7] LXA4 also decreased expression of IL-1β, TNF-α, Notch-1, Hes1, iNOS, and CD32-markers of the M1 microglia phenotype-while upregulating Hes5, Arg-1, and CD206, which are associated with the M2 phenotype. These findings suggest that LXA4 regulates microglial polarization after injury via the Notch signaling pathway.[8] Beyond the eye, LXA4 exerts neuroprotective effects within the central nervous system, including in uveitis.[9] In another study, reduced LXA4 levels were observed in patients with posterior segment uveitis, while LXA4-deficient

Corresponding author: Undurti Narasimha Das, Department of Pharmacology, Atatürk University Faculty of Medicine, Erzurum, Türkiye
e-mail: undurti@lipidworld.com

Received: July 16, 2025 **Accepted:** August 13, 2025 **Available Online Date:** 31.10.2025 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-7-161
Available at www.balkanmedicaljournal.org

ORCID iD of the author: U.N.D. 0000-0002-0191-9508.

Cite this article as: Das UN. Lipoxin A4 (LXA4) as a Potential Drug for Autoimmune Uveitis. Balkan Med J.; 2025; 42(6):579-81.

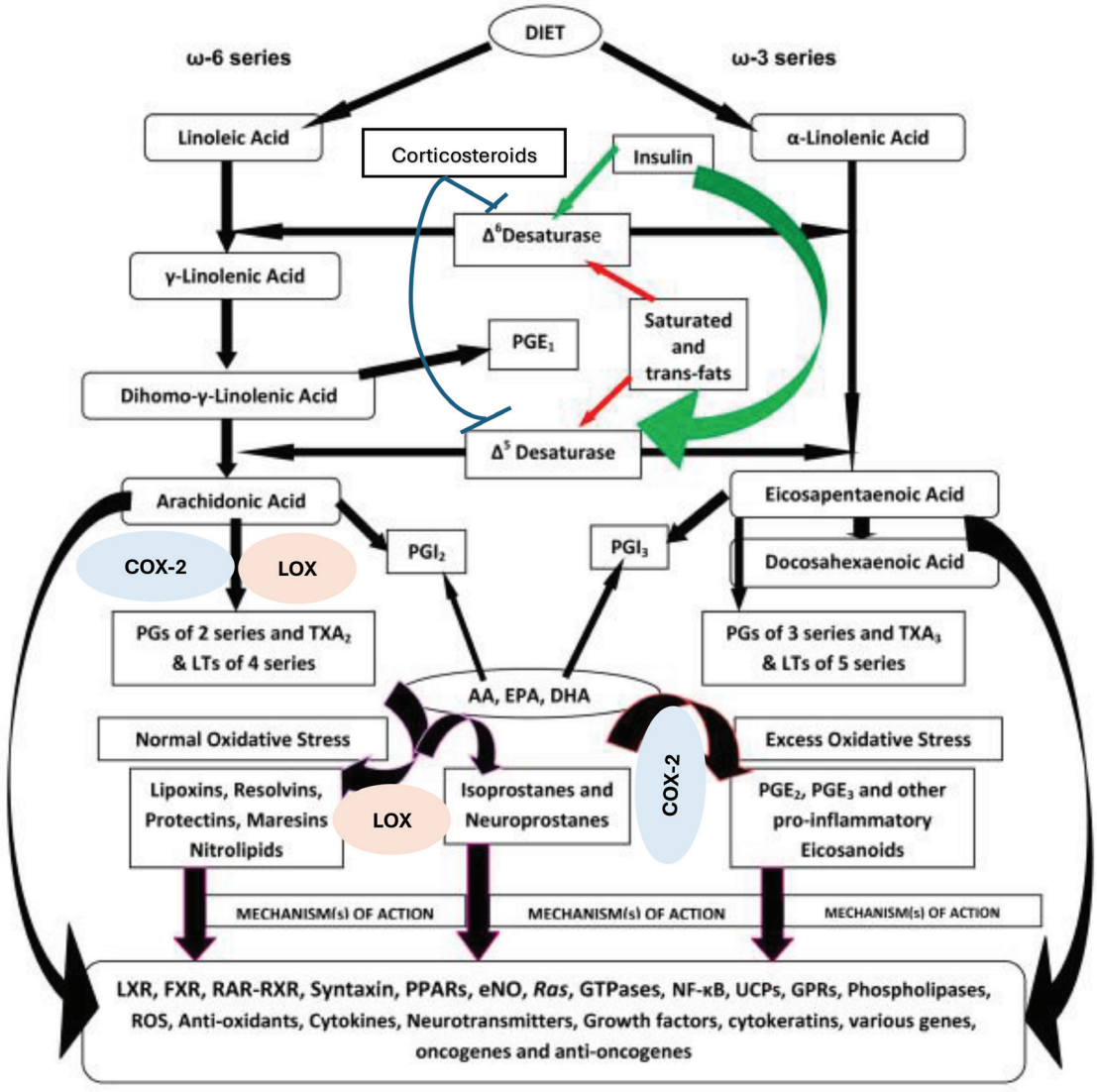

FIG. 1. Metabolism of essential fatty acids and their metabolites.
Prostaglandins (PGs) of 2 series, thromboxanes of (TXs) 2 series and leukotrienes (LTs) of 4 series derived from AA are pro-inflammatory in nature.
PGs of 3 series and TXs of 3 series, and LTs of 5 series are derived from EPA (eicosapentaenoic acid) are also pro-inflammatory in nature but are much less potent compared to those derived from AA.
LXA4 (lipoxin A4) is derived from AA and is a potent anti-inflammatory compound.
Resolvins of E series are derived from EPA which are also potent anti-inflammatory in nature.
Resolvins of D series, protectins and maresins are derived from DHA (docosahexaenoic acid) and are all anti-inflammatory compounds.

EPA, eicosapentaenoic acid, COX-2, cyclooxygenase-2, AA, arachidonic acid.

mice exhibited amplified T-cell effector function, migration, and glycolytic activity that correlated with severe pathology. In contrast, LXA4 treatment attenuated disease severity.[10] Furthermore, LXA4 was shown to regulate natural killer cell and type 2 innate lymphoid cell activation.[11] Importantly, LXA4 dampens T effector cell responses in autoimmune uveitis. Topical application of LXA4 (10 ng/eye) inhibited LPS-induced IL-1β, TNF-α, PGE2, and the expression of COX-2, VEGF, NF-κB, and c-JUN as effectively as corticosteroids (200 μg/eye). This suggests that LXA4 may be a promising therapeutic candidate for ocular inflammatory conditions, including uveitis.[12,13] Similar anti-inflammatory effects have also been reported for resolvin D1.[14,15]

Taken together, these findings highlight that LXA4, along with resolvins, protectins, and maresins, play a critical role in the pathobiology of uveitis and may serve as an endogenous cytoprotective, neuroprotective, and anti-inflammatory mediator.

Further studies are clearly needed. It would be valuable to measure tear fluid, vitreous, and plasma levels of LXA4, resolvins,

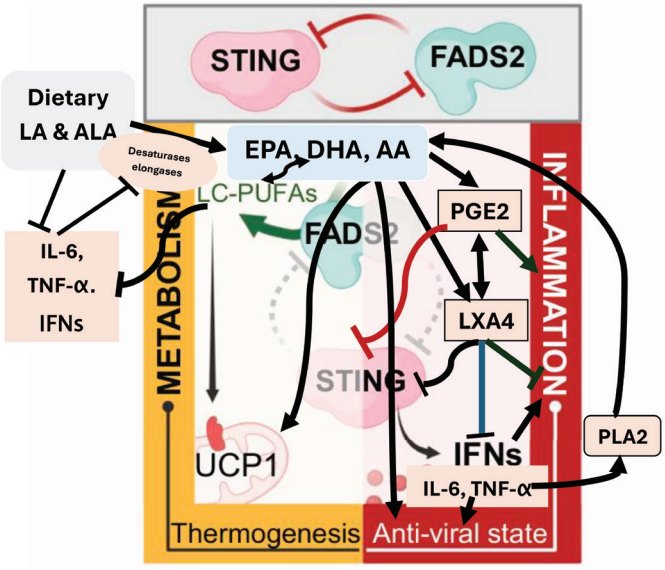

FIG. 2. Scheme showing interaction(s) between cGAS-STING pathway and EFAs and its relationship with cytokines, metabolism and thermogenesis. The *stimulator of interferon (STING)* genes regulates cytoplasmic nucleic acid [such as micronucleus (MN)] associated inflammatory responses. STING regulates polyunsaturated fatty acids (PUFAs or EFAs) metabolism and EFAs and their metabolites inhibit STING-dependent inflammation. This cross regulation is central to the maintenance of metabolic homeostasis, inflammatory events and immune responses. The protein encoded by the *FADS2* gene is a member of the *fatty acid desaturase (FADS)* gene family that acts on EFAs to convert them to their long-chain metabolites. MN containing cells are increased in uveitis. EFAs and their long-chain metabolites have anti-viral, anti-diabetic and immune and inflammation regulatory functions.

EFA, essential fatty acid; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha, DHA, docosahexaenoic acid; AA, arachidonic acid; LA, linoleic acid, ALA, alpha-linolenic acid.

protectins, and maresins and to correlate these concentrations with IL-6, TNF-α, MIF, and the expression of NF-κB, desaturases, COX-2, and lipoxygenases. Definitive clinical studies are required to evaluate the effects of intravitreal and topical administration of LXA4, resolvins, protectins, and maresins in order to determine which of these endogenous anti-inflammatory mediators are most effective. Should topical application prove beneficial, it could mark a new era in the prevention and management of uveitis and other inflammatory eye diseases.

Acknowledgements: Dr. (Prof.) UND was in receipt of visiting fellowship from TUBİTAK of Türkiye during the tenue of this study.

REFERENCES

1. Das UN. Pro- and anti-inflammatory bioactive lipids imbalance contributes to the pathobiology of autoimmune diseases. *Eur J Clin Nutr.* 2023;77:637-651. [CrossRef]
2. Shi Y, Pan H, Zhang HZ, Zhao XY, Jin J, Wang HY. Lipoxin A4 mitigates experimental autoimmune myocarditis by regulating inflammatory response, NF-κB and PI3K/Akt signaling pathway in mice. *Eur Rev Med Pharmacol Sci.* 2017;21:1850-1859. [CrossRef]
3. Loynes CA, Lee JA, Robertson AL, et al. PGE2 production at sites of tissue injury promotes an anti-inflammatory neutrophil phenotype and determines the outcome of inflammation resolution in vivo. *Sci Adv.* 2018;4:eaar8320. [CrossRef]
4. Gilroy DW, Colville-Nash PR, Willis D, Chivers J, Paul-Clark MJ, Willoughby DA. Inducible cyclooxygenase may have anti-inflammatory properties. *Nat Med.* 1999;5:698-701. [CrossRef]
5. Dai S, Zhu M, Wu R, et al. Lipoxin A4 Suppresses IL-1β-induced cyclooxygenase-2 expression through inhibition of p38 MAPK activation in endometriosis. *Reprod Sci.* 2019;26:1640-1649. [CrossRef]
6. Das UN. Essential fatty acids and their metabolites in the pathobiology of inflammation and its resolution. *Biomolecules.* 2021;11:1873. [CrossRef]
7. Livne-Ba, I, Maurya S, Gronert K, Sivak JM. Lipoxins A4 and B4 inhibit glial cell activation via CXCR3 signaling in acute retinal neuroinflammation. *J Neuroinflammation.* 2024;21:18. [CrossRef]
8. Li QQ, Ding DH, Wang XY, Sun YY, Wu J. Lipoxin A4 regulates microglial M1/M2 polarization after cerebral ischemia-reperfusion injury via the Notch signaling pathway. *Exp Neurol*. 2021;339:113645. [CrossRef]
9. Wei J, Mattapallil MJ, Horai R, et al. A novel role for lipoxin A4 in driving a lymph node-eye axis that controls autoimmunity to the neuroretina. *Elife.* 2020;9:e51102. [CrossRef]
10. Barnig C, Cernadas M, Dutile S, et al. Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. *Sci Transl Med*. 2013;5:174ra26. [CrossRef]
11. Wei J, Horai R, Jittayasothorn Y, et al. Lipoxin A4 regulates T effector cell trafficking in autoimmune uveitis. *Investigative Ophthalmol Visual Sci.* 2019;60:1350. [CrossRef]
12. Medeiros R, Rodrigues GB, Figueiredo CP, et al. Molecular mechanisms of topical anti-inflammatory effects of lipoxin A(4) in endotoxin-induced uveitis. *Mol Pharmacol.* 2008;74:154-161. [CrossRef]
13. Settimio R, Clara DF, Franca F, Francesca S, Michele D. Resolvin D1 reduces the immunoinflammatory response of the rat eye following uveitis. *Mediators Inflamm.* 2012;2012:318621. [CrossRef]
14. Rossi S, Di Filippo C, Gesualdo C, et al. Interplay between intravitreal RvD1 and local endogenous sirtuin-1 in the protection from endotoxin-induced uveitis in rats. *Mediators Inflamm.* 2015;2015:126408. [CrossRef]
15. Rossi S, Di Filippo C, Gesualdo C, et al. Protection from endotoxic uveitis by intravitreal Resolvin D1: involvement of lymphocytes, miRNAs, ubiquitin-proteasome, and M1/M2 macrophages. *Mediators Inflamm*. 2015;2015:149381. [CrossRef]