Lipoxin A₄: a novel anti-inflammatory molecule?

Arachidonic acid is metabolised by the cyclooxygenase pathway to the prostaglandins and thromboxane A₂ or via one of the lipoxygenase pathways. Three major lipoxygenase pathways have been identified in mammalian tissue – namely, the 5-, 12-, and 15-lipoxygenases. The 5-lipoxygenase pathway metabolises arachidonic acid through two intermediates, 5-hydroperoxyicosatetraenoic acid (5-HPETE) and leukotriene A₄ (LTA₄), to LTB₄ and the sulphidopeptide leukotrienes LTC₄, LTD₄, and LTE₄. The sulphidopeptide leukotrienes are potent spasmodgens for non-vascular smooth muscle and may play a part in the pathogenesis of bronchial asthma.

The interactions between 5-lipoxygenase and 15-lipoxygenase on arachidonic acid metabolism have recently been studied and a new series of biologically active metabolites described. Unlike leukotrienes, lipoxins possess a conjugated tetraene structure and the stereochemistries of the two major isomers, lipoxin (LX)A₄ and LXBr, are S₁₀, 6R, 5S-trihydroxy 7,9,13-nor-11-cis-eicosatetraenoic acid and 5S, 14B, 15S-trihydroxy 8,10,12-cis-eicosatetraenoic acid, respectively. It is now established that lipoxins can also be generated by an interaction between the 5- and 12-lipoxygenases, when the 12-lipoxygenase acts with a C₁₅-15 specificity.

Lipoxins can be generated by human neutrophils, eosinophils, or platelets from both endogenous or exogenous substrates in vitro. Furthermore, using gas chromatography and mass spectrometry with selective ion monitoring, LX₄ has been detected in the bronchoalveolar lavage fluid in patients suffering from pulmonary sarcoidosis, infective bronchopneumonia, asthma, and carcinoma of the lung. It was not detected in normal subjects. In patients with detectable LX₄ in bronchoalveolar lavage fluid, the ratio of the concentrations of LX₄ to those of sulphidopeptide leukotrienes ranged from 1:9 to 1:1 (mean 19:0), indicating that LX₄ is generated in vivo.

In vitro studies with guinea pig parenchymal lung strips have shown that lipoxins exhibit contractile activity. LX₄ prepared by total chemical synthesis has been shown to constrict parenchymal strips over a concentration range of 1 x 10⁻⁸ to 1 x 10⁻⁵ M. The contractile activity of LX₄ was slow in onset and did not plateau for 20 minutes, and was approximately 10,000 times less potent than that of LTD₄. The contraction was not mediated through secondary generation of cyclooxygenase metabolites or secondary release of sulphidopeptide leukotrienes. The activity of LX₄ may be elicited via an interaction with an LTD₄ receptor. This suggestion was further supported when it was shown that LX₄ (1 x 10⁻⁷ M) prevented mesangial cell inositol triphosphate generation induced by LTD₄.

At concentrations of 1 x 10⁻⁸ M and 5 x 10⁻⁹ M LX₄ induced the generation of mesangial cell inositol triphosphate which was abolished with a sulphidopeptide leukotriene antagonist SK&F 104353. LX₄ competed with [³H] LTD₄ for specific binding to cultured rat glomerular mesangial cells. In vivo it antagonised LTD₄-induced falls in glomerular filtration rate. Dahlen and coworkers have reported that LX₄ at a concentration of 1 x 10⁻⁶ M was able to shift the log dose-response curve of LTD₄ on guinea pig lung strip to the right. Bjork and coworkers showed that LX₄ (1 x 10⁻⁷ M) antagonised contractile 1 M and 30 x 10⁻⁶ M produced a dose-dependent contraction of human bronchi and antagonised LTC₄-induced contractions. These studies support the view that LX₄ may act as a partial agonist at the same or similar site as the sulphidopeptide leukotrienes.

The fact that 15-lipoxygenase is abundant in lung tissue and that LX₄ has been recovered in the bronchoalveolar lavage fluid of patients with asthma and other lung diseases suggests that LX₄ may be a potential mediator or modulator of inflammation in the lung. In a recent study eight subjects underwent inhalation challenge with LX₄, but no effect was seen on specific conductance, rate of airflow at 25% vital capacity (V₁₅), blood pressure, pulse, or asthmatic symptoms. There was, however, a significant shift of the specific conductance and V₁₅ dose-response curve to the right after inhalation challenge with LTC₄ combined with LX₄ compared with that after inhalation challenge with LTC₄ alone. Thus, LX₄ may modulate LTC₄-induced airway obstruction in vivo and may act as an endogenous sulphidopeptide leukotriene receptor antagonist.

Further evidence for the anti-inflammatory properties of LX₄ was suggested by the finding that prior exposure of neutrophils or eosinophils to 10⁻⁹-10⁻¹⁰ M LX₄ inhibited the chemotactic responsiveness to LTBr, formyl-methionyl-leucyl-phenylalanine (FMLP), and plasma activating factor in a dose-dependent manner.

There is limited information on the mechanisms for the inhibiting effects of LX₄ on neutrophil functions. The inhibition of chemotactic responses was associated with a concentration-dependent inhibition of phosphoinositol hydrolysis and calcium mobilisation. There was no effect on specific binding of [³H] LTBr to neutrophils following preincubation with LX₄, suggesting that the mechanism of the chemotactic factor-induced phosphoinositol hydrolysis was at a post-receptor level. Structure function studies on the mechanism of inhibition of LX₄ on LTBr-induced neutrophil migration and plasma leakage in the hamster cheek pouch model also supports its putative anti-inflammatory role.

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Successful elucidation of the mechanism(s) for the inhibitory activity of LX₄ may provide a novel therapeutic approach in inflammatory diseases.

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Lipoxin A4: a novel anti-inflammatory molecule?

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