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 lipoxigenase pathways. Three major lipoxigenase pathways have been identified in mammalian tissue – namely, the 5-, 12-, and 15-lipoxigenases. The 5-lipoxigenase pathway metabolises arachidonic acid through two intermediates, 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and leukotriene A₄ (LTxA₄) to LTD₄ and the sulphidopeptide leukotrienes LTC₄, LTD₄, and LTE₄. The sulphidopeptide leukotrienes are potent spasmones for non-vascular smooth muscle and may play a part in the pathogenesis of bronchial asthma.

The interactions between 5-lipoxigenase and 15-lipoxigenase 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 (LXA₄) and LXB₄, are S₅, 6R, 5S-trihydroxy 7, 9, 13-nor-11-cis-eicosatetraenoic acid and S₅, 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-lipoxigenases, when the 12-lipoxigenase 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, LXA₄ 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 LXA₄ in bronchoalveolar lavage fluid, the ratio of the concentrations of LXA₄ to those of the sulphidopeptide leukotrienes ranged from 0.005 to 0.3 (mean 0.19-0.4), indicating that LXA₄ is generated in vivo.

In vitro studies with guinea pig parenchymal lung strips have shown that lipoxins exhibit contractile activity. LXA₄ prepared by total chemical synthesis has been shown to constrict parenchymal strips over a concentration range of 1 × 10⁻⁸ to 1 × 10⁻³ M. The contractile activity of LXA₄ 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 LXA₄ may be elicited via an interaction with an LTD₄ receptor. This suggestion was further supported when it was shown that LXA₄ (1 × 10⁻⁷ M) prevented mesangial cell inositol trisphosphate generation induced by LTD₄. At concentrations of 1 × 10⁻⁸ M and 5 × 10⁻⁸ M LXA₄ induced the generation of mesangial cell inositol trisphosphate which was abolished with a sulphidopeptide leukotriene antagonist SK&F 104353. LXA₄ 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 LXA₄ at a concentration of 1 × 10⁻⁶ M was able to shift the log dose-response curve of LTC₄ on guinea pig lung strip to the right. Moreover, in mesangial strips cultured in the presence of 1 × 10⁻⁶ M and 30 × 10⁻⁶ M produced a dose-dependent contraction of human bronchi and antagonised LTC₄-induced contractions. These studies support the view that LXA₄ may act as a partial agonist at the same or similar site as the sulphidopeptide leukotrienes.

The fact that 15-lipoxigenase is abundant in lung tissue and that LXA₄ has been recovered in the bronchoalveolar lavage fluid of patients with asthma and other lung diseases suggests that LXA₄ may be a potential mediator or modulator of inflammation in the lung. In a recent study eight subjects underwent inhalation challenge with LXA₄, but no effect was seen on specific conductance, rate of airflow at 25% vital capacity (V₁₂₅), blood pressure, pulse, or asthmatic symptoms. There was, however, a significant shift of the specific conductance and V₁₂₅ dose-response curve to the right after inhalation challenge with LTC₄ combined with LXA₄ compared with that after inhalation challenge with LTC₄ alone. Thus, LXA₄ 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 LXA₄ was suggested by the finding that prior exposure of neutrophils or eosinophils to 10⁻⁸ to 10⁻¹⁰ M LXA₄ inhibited the chemotactic responsiveness to LTD₄, formyl-methionyl-leucyl-phenylalanine (FMLP), and plasma activating factor in a dose-dependent manner. The finding that LXA₄ attenuated LTD₄-induced neutrophil migration and plasma leakage in the hamster cheek pouch model also supports its putative anti-inflammatory role.

There is limited information on the mechanisms for the inhibiting effects of LXA₄ on neutrophil functions. The inhibition of chemotactic responses was associated with a concentration-dependent inhibition of phosphoinositide hydrolysis and calcium mobilisation. There was no effect on specific binding of [³H]LTD₄ to neutrophils following preincubation with LXA₄, suggesting that the mechanism of the chemotactic factor-induced phosphoinositide hydrolysis was at a post-receptor level. Structure function studies on the mechanism of inhibition of LXA₄ on LTD₄-induced neutrophil migration demonstrated the importance of two adjacent free hydroxy groups in either the R or the S configuration; one hydroxy group has to be in a C-6 position, but the other hydroxy group can be in either the C-5 or the C-7 position for conferment of inhibitory activity.

Successful elucidation of the mechanism(s) for the inhibitory activity of LXA₄ may provide novel therapeutic approach in inflammatory diseases.

Department of Allergy and Respiratory Medicine, UMDS, Guy's Hospital, London SE1 9RT, UK

TAK H LEE


Lipoxin A4: a novel anti-inflammatory molecule?

T H Lee

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