Lipoxin \( \text{A}_4 \): a novel anti-inflammatory molecule?

Arachidonic acid is metabolised by the cyclooxygenase pathway to the prostaglandins and thromboxane \( \text{A}_2 \) or via one of the lipoxygenase pathways.\(^1\) Three major lipoxygenase pathways have been identified in mammalian tissue – namely, the 5-, 12-, and 15-lipoxygenases.\(^2\) The 5-lipoxygenase pathway metabolises arachidonic acid through two intermediates, 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and leukotriene \( \text{A}_4 \) (LTA\(_4\)), to LT\(_B_2\) and the sulphidopeptide leukotrienes LT\(_{C\alpha}\), LT\(_{D\alpha}\) and LT\(_{E\alpha}\).\(^3\) The sulphidopeptide leukotrienes are potent spasmogens\(^4\) for non-vascular smooth muscle and may play a part in the pathogenesis of bronchial asthma.\(^5\)\(^6\)

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.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\) These molecules have been termed lipoxins. Unlike leukotrienes lipoxins possess a conjugated tetraene structure and the stereochemistries of the two major isomers, lipoxin (LX)\(_{A4}\) and LX\(_{B4}\), are \( \text{S}_2\), \( \text{R}_2 \), \( \text{SS}-\)trihydroxy 7,9,13-nor-11-\( \text{E}\)-icosatetraenoic acid and \( \text{S}_2\), \( \text{R}_2\), 14B, 15S-trans-8,12-nor-10-\( \text{E}\)-icosatetraenoic acid, respectively.\(^1\)\(^3\)\(^4\) 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 \( \text{C}_15\) specificity.

Lipoxins can be generated by human neutrophils, eosinophils, or platelets from both endogenous or exogenous substrates in vitro.\(^1\)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\) Furthermore, using gas chromatography and mass spectrometry with selective ion monitoring, \( \text{LXA}_4\) has been detected in the bronchoalveolar lavage fluid in patients suffering from pulmonary sarcoidosis, infective bronchopneumonia, asthma, and carcinoma of the lung.\(^7\) It was not detected in normal subjects. In patients with detectable \( \text{LXA}_4\) in bronchoalveolar lavage fluid, the ratio of the concentrations of \( \text{LXA}_4\) to those of sulphotripeptide leukotrienes ranged from 1:3 to 1:9 to 1:20 (mean 19:0), indicating that \( \text{LXA}_4\) is generated in vivo.

In vitro studies with guinea pig parenchymal lung strips have shown that lipoxins exhibit contractile activity.\(^1\)\(^6\)\(^9\) \( \text{LXA}_4\) prepared by total chemical synthesis has been shown to constrict parenchymal strips over a concentration range of \( 1 \times 10^{-8}\) to \( 1 \times 10^{-5}\) M.\(^1\)\(^6\)\(^9\) The contractile activity of \( \text{LXA}_4\) was slow in onset and did not plateau for 20 minutes, and was approximately 10 000 times less potent than that of LT\(_{D\alpha}\). The contraction was not mediated through a secondary generation of cyclooxygenase metabolites or secondary release of sulphotripeptide leukotrienes. The activity of \( \text{LXA}_4\) may be elicited via an interaction with an LT\(_{D\alpha}\) receptor. This suggestion was further supported when it was shown that \( \text{LXA}_4\) (\( 1 \times 10^{-7}\) M) prevented mesangial cell inositol triphosphate generation induced by LT\(_{D\alpha}\).\(^2\)\(^0\)

At concentrations of \( 1 \times 10^{-8}\) M and \( 5 \times 10^{-8}\) M \( \text{LXA}_4\) induced the generation of mesangial cell inositol triphosphate which was abolished with a sulphidopeptide leukotriene antagonist SK&F 104353. \( \text{LXA}_4\) competed with [\( \text{H}\)]LT\(_{D\alpha}\) for specific binding to cultured rat glomerular mesangial cells. In vivo it antagonised LT\(_{D\alpha}\)-induced falls in glomerular filtration rate. Dahlen and coworkers have reported that \( \text{LXA}_4\) at a concentration of \( 1 \times 10^{-6}\) M was able to shift the log dose-response curve of LT\(_{C\alpha}\) on guinea pig lung strip to the right.\(^2\) Björk and coworkers showed that \( \text{LXA}_4\) at a concentration of \( 1 \times 10^{-7}\) M \( \times 30 \times 10^{-8}\) M produced a dose-dependent contraction of human bronchi and antagonised LT\(_{C\alpha}\)-induced contractions.\(^2\) These studies support the view that \( \text{LXA}_4\) may act as a partial agonist at the same or similar sites as the sulphidopeptide leukotrienes.

The fact that 15-lipoxygenase is abundant in lung tissue and that \( \text{LXA}_4\) has been recovered in the bronchoalveolar lavage fluid of patients with asthma and other lung diseases suggests that \( \text{LXA}_4\) may be a potential mediator or modulator of inflammation in the lung. In a recent study eight subjects underwent inhalation challenge with \( \text{LXA}_4\),\(^2\)\(^3\) but no effect was seen on specific conductance, rate of airflow at 25% vital capacity (\( V_{25}\)), blood pressure, pulse, or asthmatic symptoms. There was, however, a significant shift of the specific conductance and \( V_{25}\) dose-response curve to the right after inhalation challenge with LT\(_{C\alpha}\) combined with \( \text{LXA}_4\) compared with that after inhalation challenge with LT\(_{C\alpha}\) alone. Thus, \( \text{LXA}_4\) may modulate LT\(_{C\alpha}\)-induced airway obstruction in vivo and may act as an endogenous sulphidopeptide leukotriene receptor antagonist.

Further evidence for the anti-inflammatory properties of \( \text{LXA}_4\) was suggested by the finding that prior exposure of neutrophils or eosinophils to \( 10^{-9}\) to \( 10^{-6}\) M \( \text{LXA}_4\) inhibited the chemotactic responsiveness to LT\(_{B_4}\), formyl-methionyl-leucyl-phenylalanine (FMLP), and plasma activating factor in a dose-dependent manner.\(^2\)\(^4\) The finding that \( \text{LXA}_4\) attenuated LT\(_{B_4}\)-induced neutrophil migration and plasma leakage in the hamster cheek pouch model also supports its putative anti-inflammatory role.\(^2\)\(^6\)

There is limited information on the mechanisms for the inhibiting effects of \( \text{LXA}_4\) on neutrophil functions. The inhibition of chemotactic responses was associated with a concentration-dependent inhibition of phosphoinositide hydrolysis and calcium mobilisation.\(^2\)\(^7\) There was no effect on specific binding of \([\text{H}]\)LT\(_{B_4}\) to neutrophils following preincubation with \( \text{LXA}_4\), 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 \( \text{LXA}_4\) on LT\(_{B_4}\)-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.\(^2\)\(^8\)

Successful elucidation of the mechanism(s) for the inhibitory activity of \( \text{LXA}_4\) may provide a novel therapeutic approach in inflammatory diseases.

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Lipoxin A4: a novel anti-inflammatory molecule?

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