Lipoxin A_4: a novel anti-inflammatory molecule?

Arachidonic acid is metabolised by the cyclooxygenase pathway to the prostaglandins and thromboxane 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.[2–4] The 5-lipoxygenase pathway metabolises arachidonic acid through two intermediates, 5-hydroperoxyeicosatetranoic acid (5-HPETE) and leukotriene A_4 (LTA_4), to LTB_4 and the sulphidopeptide leukotrienes LTC_4, LTD_4, and LTE_4.[5] The sulphidopeptide leukotrienes are potent spasmogens[6] for non-vascular smooth muscle and may play a part in the pathogenesis of bronchial asthma.[7–10]

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.[11 12] These molecules have been termed lipoxins. Unlike leukotrienes lipoxins possess a conjugated tetraene structure and the stereochemistries of the two major isomers, lipoxin (LX)A_4 and LXB_4, are 5S, 6R, 5S-trihydroxy 7,9,13-*trans*-11-*cis*-eicosatetraenoic acid and 5S, 14R, 15S-trihydroxy-6,10,12-*trans*-8-*cis*-eicosatetraenoic acid, respectively.[13 14] 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 C-15 specificity.

Lipoxins can be generated by human neutrophils, eosinophils, or platelets from both endogenous or exogenous substrates in vitro.[11 12 15 16] Furthermore, using gas chromatography and mass spectrometry with selective ion monitoring, LXA_4 has been detected in the bronchoalveolar lavage fluid in patients suffering from pulmonary sarcoidosis, infective bronchopneumonia, asthma, and carcinoma of the lung.[17] It was not detected in normal subjects. In patients with detectable LXA_4 in bronchoalveolar lavage fluid, the ratio of the concentrations of LXA_4 to those of sulphidopeptide leukotrienes ranges from 1·9 to 62 (mean 19·0), indicating that LXA_4 is generated in vivo.

In vitro studies with guinea pig parenchymal lung strips have shown that lipoxins exhibit contractile activity.[18 19] LXA_4 prepared by total chemical synthesis has been shown to constrict parenchymal strips over a concentration range of 1×10^{-8} to 1×10^{-5} M.[19] The contractile activity of LXA_4 was slow in onset and did not plateau for 20 minutes, and was approximately 10 000 times less potent than that of LTD_4. The contraction was not mediated through secondary generation of cyclooxygenase metabolites or secondary release of sulphidopeptide leukotrienes. The activity of LXA_4 may be elicited via an interaction with an LTD_4 receptor. This suggestion was further supported when it was shown that LXA_4 (1×10^{-7} M) prevented mesangial cell inositol triphosphate generation induced by LTD_4.[20] At concentrations of 1×10^{-8} M and 5×10^{-8} M LXA_4 induced the generation of mesangial cell inositol triphosphate which was abolished with a sulphidopeptide leukotriene antagonist SK&F 104353. LXA_4 competed with [^{3}H] LTD_4 for specific binding to cultured rat glomerular mesangial cells. In vivo it antagonised LTD_4-induced falls in glomerular filtration rate. Dahlen and coworkers have reported that LXA_4 at a concentration of 1×10^{-6} M was able to shift the log dose-response curve of LTC_4 on guinea pig lung strip to the right.[21] Bjork and coworkers showed that LXA_4 at concentrations between 1 M and 30×10^{-6} M produced a dose-dependent contraction of human bronchi and antagonised LTC_4-induced contractions.[22] These studies support the view that LXA_4 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 LXA_4 has been recovered in the bronchoalveolar lavage fluid of patients with asthma and other lung diseases suggests that LXA_4 may be a potential mediator or modulator of inflammation in the lung. In a recent study eight subjects underwent inhalation challenge with LXA_4,[23] but no effect was seen on specific conductance, rate of airflow at 25% vital capacity ($\dot{V}_{25}$), blood pressure, pulse, or asthmatic symptoms. There was, however, a significant shift of the specific conductance and $\dot{V}_{25}$ dose-response curve to the right after inhalation challenge with LTC_4 combined with LXA_4 compared with that after inhalation challenge with LTC_4 alone. Thus, LXA_4 may modulate LTC_4-induced airway obstruction in vivo and may act as an endogenous sulphidopeptide leukotriene receptor antagonist.

Further evidence for the anti-inflammatory properties of LXA_4 was suggested by the finding that prior exposure of neutrophils or eosinophils to 10^{-9}–10^{6} M LXA_4 inhibited the chemotactic responsiveness to LTB_4, formyl-methionyl-leucyl-phenylalanine (FMLP), and plasma activating factor in a dose-dependent manner.[24 25] The finding that LXA_4 attenuated LTB_4-induced neutrophil migration and plasma leakage in the hamster cheek pouch model also supports its putative anti-inflammatory role.[26]

There is limited information on the mechanisms for the inhibiting effects of LXA_4 on neutrophil functions. The inhibition of chemotactic responses was associated with a concentration-dependent inhibition of phosphoinositide hydrolysis and calcium mobilisation.[27] There was no effect on specific binding of [^{3}H] LTB_4 to neutrophils following preincubation with 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 LXA_4 on LTB_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.[28]

Successful elucidation of the mechanism(s) for the inhibitory activity of LXA_4 may provide a novel therapeutic approach in inflammatory diseases.

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