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Available online August 3, 2004.
doi:10.1016/j.jaci.2004.05.063

Lipoxins in asthma

To the Editor:

We read with great interest the article of Kowalski et al,¹ which is published in one of the latest issues of the Journal. In their trial they assessed generation of lipoxin (lipoxin A₄ [LXA₄]), 15-hydroxyeicosatetraenoic acid (HETE), cysteinyl leukotrienes (cysLTs), and prostaglandin (PG) E₂ by peripheral blood leukocytes from subjects with aspirin-induced asthma (AIA) and those with aspirin-tolerant asthma (ATA) and modulation of 15-HETE and LXA₄ generation by a PGE₁ analogue (misoprostol). They showed that the baseline level of LXA₄ of the patients with AIA was lower than that in patients with ATA.

Another interesting point in the study is that misoprostol inhibited the release of 15-HETE. They also pointed out that this release was not through an aspirin-induced COX-2 pathway because of a lack of effect on release of 15-HETE after stimulation with the specific COX-2 inhibitor celecoxib. As a result of all these findings, they concluded that decreased levels of endogenous PGE₂ in patients with AIA caused the majority of reactions observed in these patients. In our previous trial we demonstrated the inhibitory effect of PGE₂ on *in vitro* release of CysLTs.²

The role of lipoxins in the pathogenesis of AIA and ATA is a current topic of interest. Lipoxins are a structurally unique class of eicosanoids that are produced by a variety of tissues, including airway tissue.³ Lipoxins requires 15-lipoxygenase (LO) and 5-LO enzymes for synthesis. LXA₄ binds not only to its specific receptor, ALX, but also to cysLT receptor 1. The inflammatory actions of cysLTs in asthmatic patients are well defined. Increased levels of cysLTs promote airway edema, mucus hypersecretion, eosinophilic inflammation, and cytokine production by T_H2 cells.^{4,5} The interaction of LXA₄ with cysLT receptor 1 on the cell surface provides functional antagonism of cysLTs. In contrast to cysLTs, lipoxins inhibit bronchoconstriction⁶ and carry anti-inflammatory signals. Such an effect is good for asthma—lipoxins are called “good lipids” for asthma—and their therapeutic use is a current topic of interest.^{7,8} A recent trial in a murine model of asthma demonstrated that administration of stable LXA₄ analogue blocked airway hyperresponsiveness and pulmonary infiltration.⁹

In their trial Kowalski et al¹ showed a lower baseline level of LXA₄ in patients with AIA compared with that seen in those with ATA in accordance with the trial of Sanak et al.¹⁰ It seems that a decreased level of LXA₄ is unique to AIA. In the latter study the study groups were homogeneous and consisted of patients with mild asthma. However, the degree of severity in groups seems not to be comparable in the study of Kowalski et al.¹ In their study asthma severity was moderate to severe in patients with AIA, whereas it was mild

to moderate for patients with ATA. Considering the effect of asthma severity on LXA₄ level, Bonnans et al¹¹ showed that in patients with ATA, those with severe disease released lower LXA₄ concentrations than patients with mild disease in the supernatants of induced sputum samples. According to the results of these 2 studies, regardless of the existence of analgesic intolerance, there seems to be a deficient release of LXA₄ in patients with severe asthma. Important questions here are whether lipoxin release differs in patients with severe asthma with and without analgesic intolerance and whether the discrepancy in patients with mild asthma with and without analgesic intolerance disappears with increasing severity of illness? The role for decreased LXA₄ release in patients with severe asthma with and without analgesic intolerance remains to be clarified. It is also not clear by which means lipoxin release is decreased in these groups of subjects. If we assume that the diminished capacity for lipoxin formation in patients with AIA is higher than in patients with ATA, does it have a role for more severe clinical expression of AIA? Further trials are needed for the clarification of the role of lipoxins in the pathogenesis of ATA and AIA.

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doi:10.1016/j.jaci.2004.06.012