Leukotriene E_4: Perspective on the forgotten mediator

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Leukotriene (LT) E_4 mediates many of the principal features of bronchial asthma, such as bronchial constriction, hyperresponsiveness, eosinophilia, and increased vascular permeability. Furthermore, it is the most stable of the cysteinyl leukotrienes (CysLTs) and can be active at the site of release for a prolonged time after its synthesis. There might be several reasons why LTE_4 has been forgotten. LTE_4 demonstrated low affinity for $CysLT_1$ and $CysLT_2$ receptors in equilibrium competition assays. It was less potent than other CysLTs in functional assays, such as calcium flux, in cells transfected with $CysLT_1$ and $CysLT_2$. The introduction of $CysLT_1$ antagonists into clinical practice diverted interest into $CysLT_1$-related mechanisms, which were mediated mainly by LTD_4. However, experiments with animal models and human studies have revealed that LTE_4 has unique characteristics that cannot be explained by the current knowledge of $CysLT_1$ and $CysLT_2$. These activities include its potency relative to other CysLTs to increase airway responsiveness to histamine, to enhance eosinophilic recruitment, and to increase vascular permeability. Asthmatic airways also demonstrate marked *in vivo* relative hyperresponsiveness to LTE_4, especially in patients with aspirin-sensitive respiratory disease. This has stimulated a search for additional LT receptors that would respond preferentially to LTE_4 stimulation. (J Allergy Clin Immunol 2009;124:417-21.)

Key words: *Cysteinyl leukotriene, leukotriene E_4, asthma, aspirin-sensitive respiratory disease, cysteinyl leukotriene receptor*

Abbreviations used
ASRD: Aspirin-sensitive respiratory disease
CysLT: Cysteinyl leukotriene
LT: Leukotriene
SRS-A: Slow-reacting substance of anaphylaxis
$uLTE_4$: Urinary LTE_4

The cysteinyl leukotrienes (CysLTs) were discovered during the characterization of a mixture of compounds referred to as the slow-reacting substances of anaphylaxis (SRS-As). By the 1960s and 1970s, many of the biologic and physiochemical properties of the SRS-As, in particular their smooth muscle–contracting abilities, had been described. It was the lasting contractile property of SRS-As at very low concentrations that generated interest in these lipid compounds as putative mediators in bronchial asthma. By the 1980s, the covalent structure and total synthesis of SRS-As had been determined, and SRS-As were discovered to be a mixture of 3 arachidonic acid derivatives, leukotriene (LT) C_4 and its 2 metabolites, LTD_4 and LTE_4.[1-3]

The elucidation of the structures and synthetic pathways for the LTs was soon followed by a comprehensive assessment of their biologic functions. Most of the early studies focused on LTC_4 and LTD_4 and demonstrated that both compounds were very potent inducers of contraction in guinea pig airways and isolated human bronchi.[4,5] *In vivo* studies in healthy individuals confirmed that LTC_4 and LTD_4 when inhaled were thousands of times more potent than histamine in inducing airway contraction.[6,7] The biologic activities of LTE_4 have generally been studied much less, probably because it was an end product of CysLT metabolism and demonstrated lower bronchoconstrictor potency in comparison with LTC_4 and LTD_4.[8]

This review summarizes some of the activities of LTE_4 and re-examines some results of earlier studies, many of which are in human subjects, suggesting that LTE_4 is a potent mediator in its own right.

LTE_4 AND BRONCHIAL HYPERRESPONSIVENESS

Allergen challenge of lung tissue from asthmatic subjects elicits bronchial contraction that correlates with the release of LTC_4, LTD_4, and LTE_4.[9] It is interesting that all CysLTs were equally potent agonists for contraction of human bronchi in this early study. LTE_4 has also been shown to be equally effective as LTC_4 and LTD_4 in contracting human intralobar airways, suggesting that LTE_4 should be considered as a full agonist for human bronchial contraction.[10] These observations were confirmed *in vivo* by Davidson et al,[8] who demonstrated that LTE_4 is a potent bronchoconstrictor in human subjects.

Thus LTE_4 is similar to LTC_4 and LTD_4 in its bronchoconstrictor activity but, in contrast, has a unique relationship with "nonspecific" hyperresponsiveness in asthma. Although in healthy subjects inhaled LTC_4 and LTD_4 were several thousand times more potent than histamine in eliciting comparable impairment of pulmonary function, in asthmatic subjects inhaled LTC_4 and LTD_4 were only hundreds of times more potent, showing that the relative responsiveness to these 2 CysLTs when inhaled was much greater in healthy than in asthmatic subjects.[6,11,12] Furthermore, subjects who were most responsive to methacholine or histamine had the

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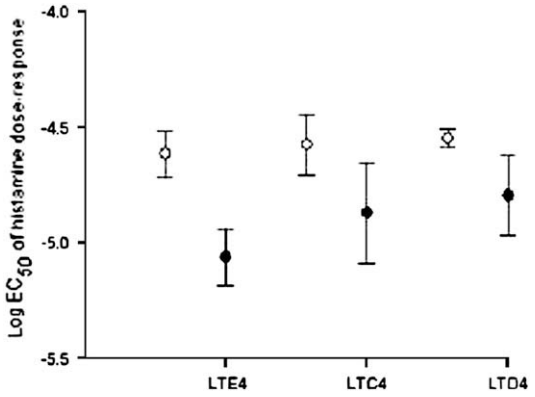

FIG 1. Log median effective concentration *(EC_{50})* of histamine dose-response effect in control guinea pig tracheas *(open circles)* and tracheas pretreated *(solid circles)* with 23 mol/L LTE_4, 80 mol/L LTC_4, and 40 mol/L LTD_4. LTE_4 (n = 8) significantly enhanced the responsiveness to histamine of tracheal smooth muscle ($P < .01$), whereas LTC_4 (n = 7) and LTD_4 (n = 7) did not elicit increased responsiveness to histamine. Reproduced with kind permission from Lee et al.[16] Copyright PNAS.

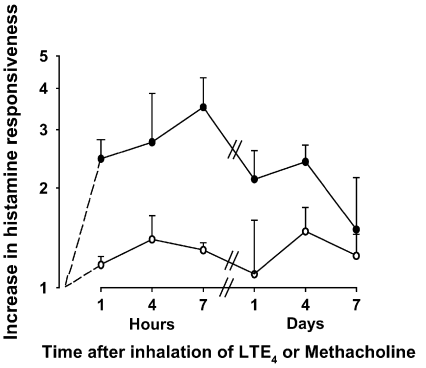

FIG 2. Time course of changes in airway histamine responsiveness after inhalation of bronchoconstricting doses of methacholine *(open circles)* and LTE_4 *(solid circles)*. Results are the geometric mean ± SEM for 4 subjects with asthma and were calculated as the ratio of the provocative dose of histamine needed to cause a 35% fall in specific airway conductance (PD_{35}) after inhalation of diluent to histamine PD_{35} after inhalation of methacholine or LTE_4. After inhalation of LTE_4, there was a time-dependent increase in histamine responsiveness that increased to a maximum of 3.5-fold at 7 hours after challenge and disappeared by 1 week. Reproduced with kind permission from Arm et al.[18] Copyright Elsevier.

lowest relative airway response to both of these LTs.[13] Of interest, the lower relative airway responsiveness to CysLTs in patients with asthma was not observed when LTE_4 was analyzed. Asthmatic subjects were 26 times more sensitive to inhaled LTE_4 than healthy subjects, whereas they were only 7 times more sensitive to methacholine and histamine, suggesting that asthmatic airways might be selectively hyperresponsive to LTE_4 in contrast to other CysLTs.[14] In addition, there was a positive correlation between airway responsiveness to LTE_4 and responsiveness to histamine and methacholine in asthmatic subjects, emphasizing a unique property of LTE_4 in patients with asthma. This observation was confirmed and extended in a subsequent study in which the relative potencies of LTC_4, LTD_4, and LTE_4 were directly compared with those of histamine and methacholine in the same healthy and asthmatic subejcts.[15] There was a substantially augmented level of hyperresponsiveness to LTE_4 in subjects with asthma, which was not observed for the other bronchoconstrictor agents, when compared with that seen in healthy subjects. Compared with healthy subjects, the airways of a group of asthmatic subjects were on average only 14-fold more responsive to inhaled histamine, 16-fold more responsive to methacholine, 6-fold more responsive to LTC_4, and 9-fold more responsive to LTD_4 but 219-fold more responsive to LTE_4. It was suggested that the mechanism of the bronchoconstriction induced by LTE_4 might be distinct from that produced by LTC_4 and LTD_4 in subjects with asthma, reflecting CysLT receptor heterogeneity in human bronchi.[15]

LTE_4 is also unusual among many other bronchoconstricting agents in its potential to enhance airway hyperresponsiveness to other agonists. It was first demonstrated in a guinea pig model that LTE_4, but not LTC_4 and LTD_4, enhanced the contractile response of tracheal spirals to histamine.[16] The ability of LTE_4 to induce hyperresponsiveness to histamine was unrelated to contractile activity because LTC_4 and LTD_4 did not elicit increased responsiveness to histamine despite constricting tracheal tissues by the same degree as LTE_4 (Fig 1). Indomethacin abolished the LTE_4–induced hyperresponsiveness to histamine but did not alter CysLT-induced contraction, thereby dissociating contraction from the capacity to enhance histamine responsiveness. It also suggested that the enhancement of airway reactivity is related to the generation of COX pathway products, whereas CysLT-elicited contraction is mediated by a mechanism independent of prostaglandin synthesis. CysLT-induced contraction was inhibited by 1 μg/mL of the SRS-A inhibitor FPL55712, whereas a 10 times higher concentration of FPL55712 was required to inhibit LTE_4-induced augmentation of responsiveness to histamine, suggesting that LTE_4-induced hyperresponsiveness and contraction might be mediated by different receptors.[16]

Studies on guinea pig tissues were confirmed in isolated human bronchus. Pretreatment of human airways with LTE_4 *in vitro* enhanced histamine responsiveness, as demonstrated by a 4-fold leftward displacement of the histamine dose–response curve.[17] This effect was blocked by the thromboxane A_2 receptor antagonist GR32191, suggesting that LTE_4-induced hyperresponsiveness to histamine in human airways is also mediated by the secondary generation of COX products. These *in vitro* observations were confirmed *in vivo* by Arm et al,[18] who reported that inhalation of LTE_4 in asthmatic but not healthy subjects elicited a time-dependent enhancement in histamine bronchial responsiveness that reached a maximum level at 7 hours after LTE_4 inhalation and could persist for up to 1 week (Fig 2). The capacity of LTE_4 to enhance airway responsiveness was specific for histamine because similar changes were not observed after methacholine challenge.[18,19] These findings suggested that LTE_4-mediated enhancement of bronchial reactivity might be agonist specific and possibly involved regulation of histamine receptor expression rather than a change in general nonspecific bronchial responsiveness. This hypothesis was supported by the finding that LTE_4 can prime histamine responses by increasing surface histamine H_1 receptor expression.[20]

The reason for the differences in response to LTE_4 between healthy and asthmatic subjects could be related to the differences in baseline airway caliber and the possible effect of this on the deposition of LTE_4 in the bronchi. However, the observation is equally consistent with the existence of increased expression of a putative LTE_4-specific receptor or signaling pathway in asthmatic subjects. A direct interaction between a putative LTE_4 receptor and histamine receptors or interaction at the level of intracellular signaling might be responsible for the experimentally observed phenomenon.