

SEX-DEPENDENT ROLE OF LEUKOTRIENES IN AIRWAY HYPERREACTIVITY AND PULMONARY INFLAMMATION IN AN EXPERIMENTAL MODEL OF ALLERGEN SENSITIZATION

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Asthma is a chronic airway inflammatory disease with higher incidence in female than male patients. Recently, sex disparities in leukotriene (LT) production have been shown in in vitro and in vivo experimental models of inflammation (Pergola et al., 2008; Pergola et al., 2011; Rossi et al., 2014). The aim of this study was to evaluate sex difference in LT production following allergen sensitization in the mouse and its correlation with cardinal features of asthma such as airway hyperreactivity and pulmonary inflammation. Moreover sex bias in the efficacy of clinically LT-modifier drugs was evaluated.

Adult female and male BALB/c mice were sensitized on days 0 and 7 by subcutaneous injection of ovalbumin (OVA) adsorbed onto Al(OH)₃ and, at different time points, LTC₄ and LTB₄ pulmonary levels were correlated to bronchial reactivity, lung inflammation and mast cell infiltration/activation. In a separate set of experiments mice were treated with montelukast sodium, zileuton and MK886.

OVA sensitization induced an increase of pulmonary LT levels only in female mice. This increase well-correlated to airway hyperreactivity (evaluated as bronchial reactivity to charbacol) and pulmonary inflammation (evaluated by hematoxylin and eosin periodic acid–Schiff staining). Also in male mice lung function was altered by sensitization but the magnitude was less marked. Accordingly mast cell recruitment (evaluated by Tryptase positive staining) and activation (evaluated by PGD₂ and IL-13 pulmonary levels) were earlier and much more evident in female. This sex bias in LT production reflected a different therapeutic response to LT-modifier drugs. In fact, montelukast sodium, zileuton and MK886 reduced OVA-induced bronchial hyperreactivity and pulmonary inflammation only in female mice.

Our data reveal significant sex differences in the biosynthesis of LTs in mouse model of asthma, associated with a different beneficial action of LT modifiers. Therefore, these results add significant insights into the understanding of basic sex differences in asthma, with possible therapeutic implications for a sex-tailored treatment.

Pergola et al. (2008) Proc Natl Acad Sci U S A. 105, 19881-6.

Pergola et al. (2011) FASEB J. 25, 3377-87.

Rossi et al. (2014) Pharmacol Res. 87, 1-7.