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**Institutionen för Medicin, Huddinge
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Studies of Exercise-induced Bronchoconstriction to Define Protective Mechanisms in Asthma

AKADEMISK AVHANDLING

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ABSTRACT

Exercise-induced bronchoconstriction (EIB) occurs in the majority of asthmatics following vigorous exercise. EIB is caused by a loss of water from the airways creating a hyperosmolar environment in the tissue that in turn triggers the release of bronchoconstrictive mediators. These bronchoconstrictive mediators, including histamine, cysteinyl leukotrienes (CysLTs) and prostaglandins, act at their respective receptors on the airway smooth muscle to induce bronchoconstriction. Because the mechanism of EIB involves drying of the airways, provocations mimicking this drying, such as eucapnic voluntary hyperpnea (EVH) and mannitol inhalation can be used to study EIB. With repeated challenge, a smaller response is observed following the second challenge and this decreased responsiveness is called refractoriness. Defining the mechanism of refractoriness may lead to new treatments for asthma.

In this thesis a range of airway challenges were performed to study the urinary excretion of mediators released in the lung following EIB and the effect of different interventions. Furthermore, urinary mediator excretion during refractoriness was also studied.

For the first time we demonstrated urinary excretion of CysLT and Prostaglandin D2 metabolites after EVH. Mediator release was no different in subjects who did not experience bronchoconstriction following EVH compared to those who did react with bronchoconstriction. This indicates that a necessity of EIB is for the airways to be sensitive to the mediators released. Pre-treatment with the mast cell stabilising drug sodium cromoglycate (SCG) inhibited the airway response to EVH, and the inhibition was accompanied by a decreased release of mediators into the urine. The same effects were observed following pre-treatment with a single high dose of inhaled corticosteroid (ICS). Pre-treatment with fish oil, rich in omega-3 fatty acids, had no effect on the basal excretion of urinary mediators, or airway responsiveness to mannitol challenge.

We also report the novel finding of refractoriness following repeated mannitol challenge. Mast cell mediators were excreted into the urine to the same extent after both the first challenge and the repeated challenge 90 min later. Also, those that were most refractory displayed the highest mediator release. This contradicts depletion of mediator release at the time of the second challenge as being the mechanism of refractoriness. These findings were then replicated by repeated EVH challenge. We also demonstrate for the first time an extended spectrum of urinary mediators excreted following EVH. Increased levels of the bronchoprotective mediators PGE2 and PGI2 were seen, which supports the release of protective prostaglandins as being a mechanism of refractoriness.

In summary, this thesis provides evidence that the mechanism of refractoriness does not involve mediator depletion. Rather, it indicates that there is a decreased sensitivity at the level of the airway smooth muscle to the mediators released. The induction of this decreased sensitivity may include the release of PGE2 and PGI2, which are likely to mediate protective responses.