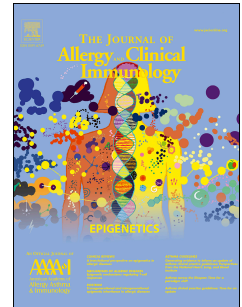


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Editorial

Mannitol and the mechanisms behind bronchoconstriction

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Mannitol is used to assess bronchial hyperresponsiveness, aiding the diagnosis of asthma (1). The mechanisms behind the bronchial response to indirect agents, such as exercise and mannitol, depend on airway inflammation. The airways of patients with asthma have been shown to have increased sensitivity to acute changes in airway osmolarity and dehydration. Exercise, as a stimulus of the airways, leads to dehydration of the airway surface followed by a local increase of osmolarity.

Likewise, inhalation of mannitol rapidly increases the osmolarity of the airway surface liquid, mimicking the effect of exercise. Several studies in asthma patients have examined the mediator release after both exercise and mannitol and the response to different pharmacological drugs. Their findings support the evidence that mannitol mimics the effect of exercise. This similarity of mechanism when testing patients with asthma increases the possibility of moving from “bed-to-bench” using the translational approach.

Anderson SD and coworkers have documented the effect on acute airway narrowing of several different drugs, such as nedocromil sodium, cromolyn sodium and antihistamines as well as chronic use of inhaled corticosteroids, and single doses of short-acting and long-acting beta2-agonists (2). Bronchoconstriction was associated with an increase in urinary excretion of the metabolites of prostaglandin D(2) (PGD₂) and leukotriene E(4) (LTE₄). Sodium cromoglycate provides some protection against inhaled mannitol and appears to do so by inhibiting the release of PGD₂, but not LTE₄, supporting the evidence that leukotriene receptor antagonist montelukast does not alter sensitivity to mannitol. This might be cell dependent. Nevertheless, it has not been documented that different types of cells are related to the specific symptoms in asthma. Interestingly, a cough variant of asthma developed during in vivo mannitol provocation was not inhibited by nedocromil, although mediator release was altered. This showed that inhibition of bronchial contraction is different from mediator release, which should be in focus when using laboratorial techniques.

Mast cells play a central role in the pathophysiology of asthma, and both the location and the density of mast cells in asthma are seemingly important for airway hyperresponsiveness (AHR) and asthma (3). Focus on the distribution of mast cells in the different airway compartments has shown an increased proportion of chymase-positive mast cells in the submucosa of asthmatic individuals with AHR compared with the proportion in their counterparts without AHR (3). This difference in the endotype of asthma could be of major importance when translating results from bench-to-bed.

Most conditions have been scientifically investigated, at least once, while the current article by Säfholm et al (4) is unique in its set-up (Table 1).

In vitro studies have demonstrated significantly increased secretion of both PGD_2 and LTC_4 in response to hyperosmolar activation of human mast cells. Guliksson et al demonstrated that both histamine and PGD_2 release was markedly elevated independent of dose, whereas LTC_4 release was found to increase dose dependently (5). In vitro methods using only inflammatory cells have thus been questioned, and new standardized methods are needed for provocation and evaluation.

In the present issue, a new in vitro testing method is proposed by Säfholm et al., where mannitol has been used as a standardized trigger of mast cell-dependent contraction of human small bronchi (4). As previously concluded, mannitol is easy to use in a clinical setting, mimics exercise-induced bronchoconstriction (EIB), and can be used in an in vitro setting. Many earlier studies have shown that different pharmacological possibilities are suitable for treating patients with EIB. However, few of these drugs are used in the clinical setting due to insufficient clinical effect compared with treatment including inhaled corticosteroids (ICS) and beta2-agonists. Daily use of ICS is needed to inhibit mediator release from mast cells; patients request the treatment when needed. However, when used frequently, beta2-agonist is not the first drug of choice owing to development of tachyphylaxis. Accordingly, new pharmaceutical studies are needed to evaluate the mechanism and the effect of drugs from bench-to-bed.

In the current study by Säfholm et al. (4), the authors show the results from a new experimental ex vivo protocol, where they studied exposure to hyperosmolar mannitol to trigger human mast cell depletion of mediators and cell-dependent smooth muscle contraction using small human bronchi. The study introduces the possibility of newer and more sophisticated studies, for example of the biologic drugs with limited action point, when examining small bronchi dissected and harvested

from patients undergoing a lobectomy. Only a small number of the patients had asthma and an obvious question is whether material taken from patients with asthma would have changed the study's results, albeit the few patients included with asthma behaved similarly to those without asthma. The current results indicate that mediator release and inhibition of response in the group of patients without asthma were dependent on the concentration of mannitol used. Conversely, Sverrild et al (6) showed that none of the control persons in their study group responded to mannitol with airway constriction; moreover, they showed a low sensitivity but a very high specificity. This illustrates the importance of patient selection. Interestingly, the response to mannitol during the first 10 minutes paralyzed the muscle contraction for the following 50 minutes. This differs from the human in vivo finding where a response to either mannitol or exercise stabilizes after 10 to 15 minutes and is totally reversed after 30 minutes in most patients. Säfholm et al. (4) elegantly demonstrated that mannitol induces mediator release originating from the mast cells within the tissue using an inhibition with relevant pharmacological drugs was shown. Notably, the effect of montelukast and cromoglycate was similar, although this is not the case in a clinical setting and the release of mediator from mast cells and the constriction of the smooth muscles might be two different issues. Mast cells are localized in different compartments of the bronchial lining, for example, the submucosal mast cells, indicating the mast cells might differ as might the mediator release (3). In Säfholm et al (4), the authors have developed a very interesting model that mimics typical factors associated with the asthmatic endotypes using small bronchi and not a cell culture, small bronchi containing epithelium, the infiltration of Th2 inflammatory cells and mast cells as well as the smooth muscle compartment all of which are integrated in the overall reaction of airway responsiveness due to mannitol. This new in vitro set-up mimics an in vivo situation that can be used when testing future drugs focusing on asthma control, indicated by negative response on mannitol. Studies such as the current in vitro test of EIB might be the first step when evaluating

effects other issues than reduction in the rate of exacerbation. Whether the inclusion of patients without asthma, as done by S  fholm et al. (4), has an impact on the results needs to be tested in a clinical setting. However, this might not be a priority because the study showed a significant association between the mediator release and the use of pharmacologic drugs after mannitol provocation. There is a difference between real-life and the laboratory-investigated findings of the effect on mast cells. These key findings in persons without asthma should be demonstrated in those with asthma to determine whether it is a matter of response level or of differences in disease pattern.

Table 1 Key Point between asthma research performed in human, animal models and in the laboratories.

Airway Responsiveness	Human	Animal model	Laboratories
Indirect testing (AHR)	Mannitol, Exercise (1)	Mouse Model (7)	Cells# Bronchial tissue (4)##
Direct testing (AHR)	Methacholine, Histamine(6)	Mouse model (7)	Bronchial biopsies (8)
Allergic	Aeroallergens	Allergen-na��ve! (9) Aerosol OVA	HDM in bronchial biopsies (8)
Non-allergic	Irritants (10)	Hapten-induced (7)* Knock-out mice	Cells and biopsies (3)
Occupational	Irritants (10)	Hapten-induced(7)	BAL fluid#

AHR: airway hyperresponsiveness, BAL: Bronchoalveolar lavage, #: Eosinophils, Neutrophils, Macrophages, ##: Mast cells, * not uniform under development, OVA: ovalbumin, ! allergen na  ve transgenic mice

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