

Letter to the Editor

House dust mite models: Will they translate clinically as a superior model of asthma?

To the Editor:

House dust mite (HDM) is a common allergen associated with allergic asthma. Consequently, HDM extracts are being more widely used to model the allergic airway phenotype. Unfortunately, as pointed out by Birrell et al,¹ there is a paucity of preclinical data demonstrating that HDM elicits classic features of allergic asthma, namely, the early and late asthmatic responses.

Currently, the primary end points assessed in these models continue to be airway inflammation and airway hyperreactivity. Neither measure is necessarily a direct indicator of allergen-specific responses in the airways, as both may certainly be the result of innate responses to components contained within the HDM extract. For instance, eosinophil numbers and T_H2 cytokine levels were increased in lavage fluid following a single HDM challenge in sham-sensitized rats, leaving some to question whether these systems are truly modeling allergic airway disease.^{1,2} That said, several groups have shown in mice that HDM induces an adaptive immune response and airway hyperreactivity in a T_H2-dependent fashion, which has been linked to innate inflammatory changes occurring after mucosal damage.^{3,4} However, no study has directly assessed whether HDM can evoke antigen-induced bronchoconstriction responses in mice.

To specifically address this problem, we assessed whether HDM could mimic the early asthmatic response (EAR) in mice. Asthmatic patients with high levels of circulating HDM-specific IgE develop acute bronchoconstriction after exposure to HDM. Mast cells and basophils degranulate to release mediators (eg, histamine and cysteinyl leukotrienes) that increase airflow resistance through a reduction in the luminal diameter of the airways as a result of airway smooth muscle contraction. In mice, allergen-induced acute bronchoconstriction has been well characterized in the classic ovalbumin model of allergic airway disease. Briefly, mice systemically sensitized (along with an adjuvant) and then topically or intravenously dosed with ovalbumin develop increased airways resistance within minutes of exposure.⁵ Of note, there are species-specific differences in how this response develops^{5,6}; instead of histamine, 5-HT is the predominant preformed mediator released from mast cells in mice and drives the EAR through a central nervous system reflex instead of a direct effect on smooth muscle.⁶ That said, the primary mechanisms driving the EAR are similar in mouse and man; the response in both species has been shown to be IgE- and mast cell mediator-dependent.⁵⁻⁷

To assess whether HDM could induce a similar type I hypersensitivity response in the airways, we intranasally administered HDM extract (25 µg) or saline to male, BALB/c mice once daily, 5 days a week, for 1 to 3 weeks. Twenty-four hours after the last administration, anesthetized mice were intravenously administered HDM (25-250 µg) and respiratory system resistance (*R*) was measured by using the flexiVent system (SCIREQ, Montreal, Quebec, Canada). Statistical significance for the experiments described below was determined by using a 2-tailed *t* test of unpaired data sets, with the exception of Fig 1, C, in which a 1-way ANOVA was used.

HDM increased *R* within minutes of the intravenous injection, which is characteristic of a mast cell-mediated response

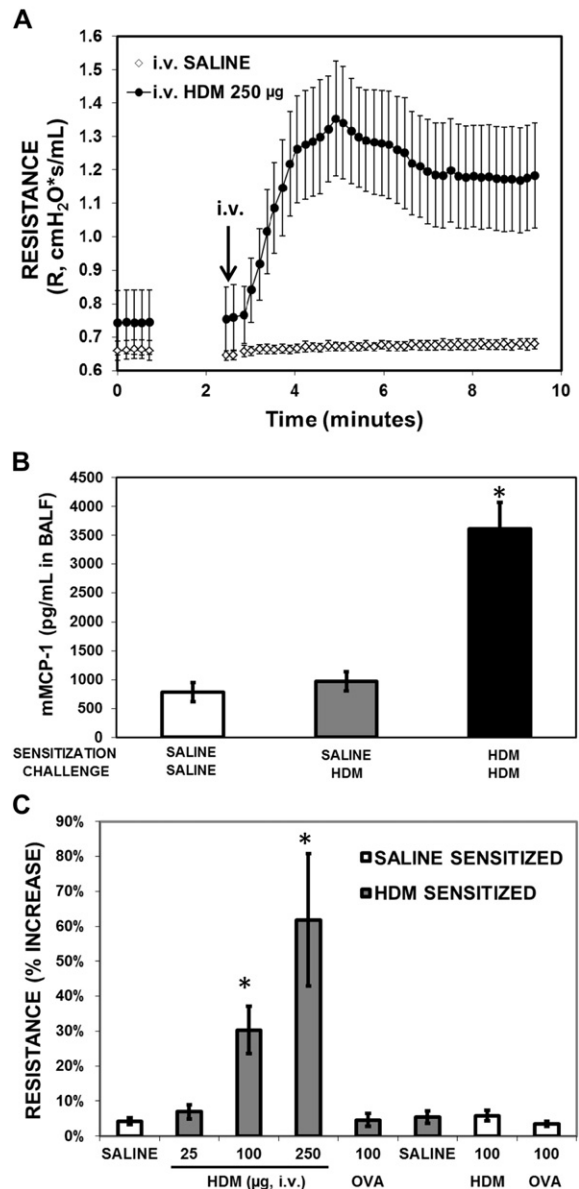


FIG 1. Intravenous administration of HDM to HDM-sensitized mice increased respiratory system resistance (*R*) (A) and mouse mast cell protease 1 (mMCP-1) levels in lavage fluid (B). C, Percent peak increase over baseline *R* to intravenous (*i.v.*) saline, ovalbumin (OVA), and dose-response to HDM in HDM sensitized and nonsensitized mice. Data are presented as mean $\pm$ SEM (*n* = 4-8). BALF, Bronchoalveolar lavage fluid.

(Fig 1, A). Consistent with this observation, increased levels of mouse mast cell protease 1 were measured in the bronchoalveolar lavage fluid of HDM-sensitized mice (*P* < .05) (Fig 1, B). Only mice previously exposed to HDM developed acute bronchoconstriction in a dose-dependent fashion (Fig 1, C). HDM-sensitized mice dosed intravenously with ovalbumin did not develop bronchoconstriction, indicating that the response was HDM-specific. Furthermore, the increased airways resistance did not develop within the first week of HDM administrations, but was measurable only after 3 weeks, suggesting that a

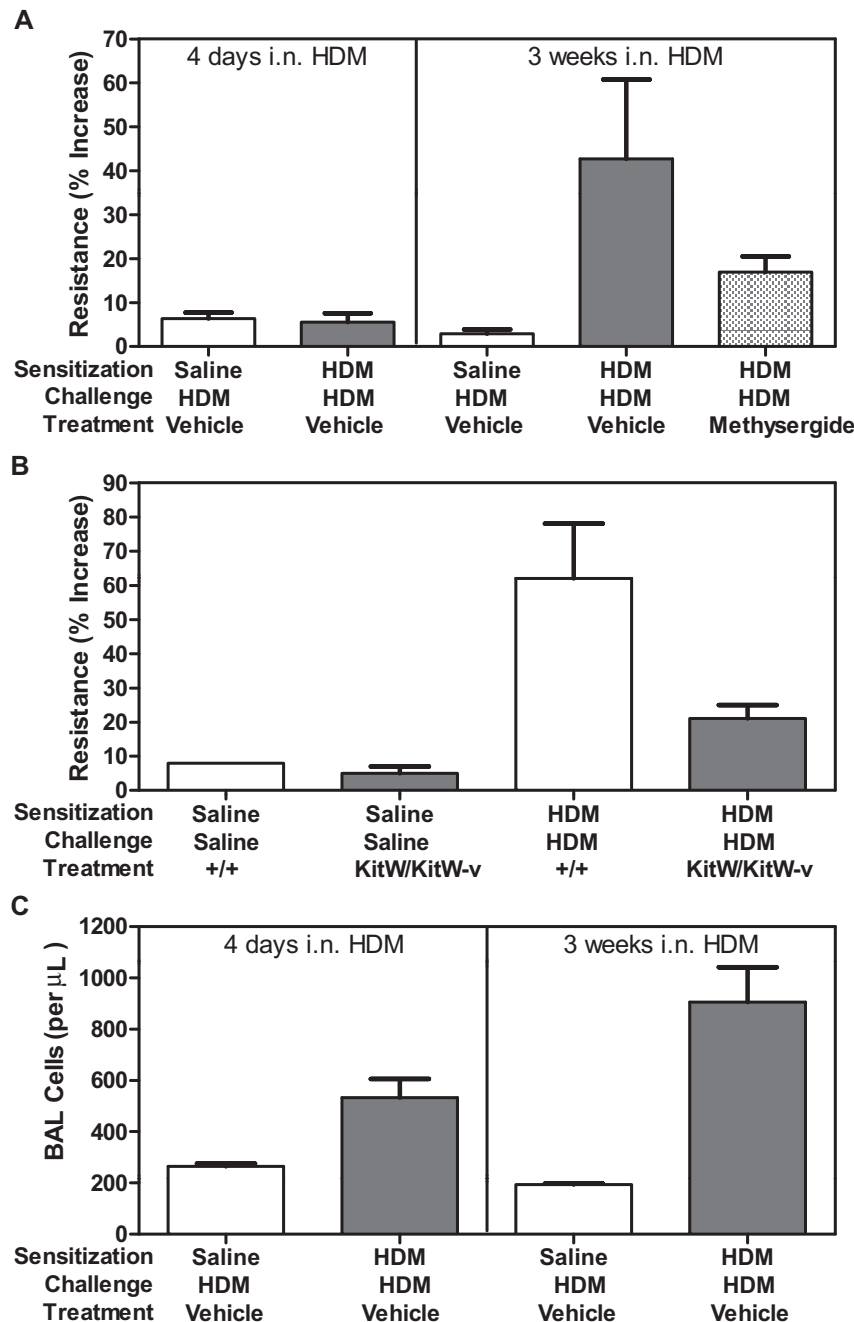


FIG 2. **A**, R increased after 3 weeks, but not 4 days, of HDM treatment and was inhibited by methysergide (10 mg/kg, i.p.) and reduced in mast cell-deficient mice (**B**). Total cells recovered in the bronchoalveolar lavage (BAL) fluid (**C**) increased after 4 days and 3 weeks of HDM treatment. Data are presented as mean $\pm$ SEM ($n = 4-8$). *i.n.*, Intranasally; *i.p.*, intraperitoneal.

time-dependent event, such as class-switch recombination, was required before allergen-induced bronchoconstriction developed (Fig 2, A). Moreover, the response was mediated in large part by serotonin most likely derived from mast cells. The 5-HT receptor antagonist methysergide dosed 1 hour prior to intravenous HDM administration significantly inhibited this response by $65\% \pm 9\%$ ($P < .05$) (Fig 2, A). Similarly, KitW/KitW-v mice that are deficient of mast cells also had an attenuated response, $71\% \pm 7\%$ lower than did their respective wild-type (WBB6F1/J) controls ($P < .05$) (Fig 2, B). Interestingly, inflammatory cell

numbers in the lavage fluid were increased after both 4 days and 3 weeks of HDM administrations ($P < .05$), indicating that a significant innate component to the inflammatory response also exists in this model (Fig 2, C).

These data clearly demonstrate that HDM can model prototypical type I hypersensitivity responses in the airways of mice sensitized through the respiratory mucosa. Specifically, we demonstrate for the first time that HDM exposures can trigger a mast cell-dependent acute bronchoconstriction characteristic of the EAR. As such, it may not be necessary to revert to systemic

sensitization methods as suggested by others.¹ HDM can mimic many key features of allergic asthma that now includes mast cell-mediated type I hypersensitivity responses in addition to mucus secretion and T_H2 cytokine production, the latter of which drives the airway hyperreactivity and airway eosinophilia in this model.³ Do these data suggest that the HDM model is simulating allergic asthma exactly as it occurs in the clinic? Most likely not, but this is no different than other models of chronic lung diseases where exposure to an etiological agent can recapitulate several disease-like features in mice (eg, the smoking model for chronic obstructive pulmonary disease).

The use of HDM to model allergic asthma will always be attractive because it is a disease-relevant antigen; however, it is clear that further characterization of the HDM model is outstanding. For instance, there is still a need to investigate the role of IgE in this model. A more comprehensive understanding of the mechanisms driving HDM-induced changes will be imperative to establish how this system can recapitulate or how it can differentiate from the features of other asthma models, as well as the disease itself. The data presented here significantly extend the current knowledge by demonstrating that HDM sensitization and challenge in mice induces a type I hypersensitivity reaction that is dependent on mast cells and can be blocked by a 5-HT receptor antagonist, methysergide. Thus, this model can be used as a preclinical translational tool that can help develop more effective drugs or therapeutic strategies for the clinical management of immediate hypersensitivity responses associated with asthma.

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