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Brief Communication

Differential Asthmatic Effect Due to House Dust Mite Depending on Age and Exposure Duration

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Asthma is a chronic lung disease characterized by wheezing, cough, and chest pain. The objective of this study was to examine asthmatic effect due to house dust mite (HDM) according to age and exposure duration. Asthma induction in young (6 weeks) and old (12 months) aged C57BL6/J mice was accomplished by HDM administration. Bronchoalveolar lavage fluid (BALF) was collected. Inflammatory cells in BALF were counted. Mucus production in lung tissues was evaluated by periodic acid Schiff (PAS) staining. Intraperitoneal (*i.p.*) and intranasal (IN) injection of HDM induced infiltration of inflammatory cells into lungs of mice. The increase of total cells was higher in young mice than in old mice. Mucus secretion from goblet cells increased after HDM administration, with young mice showing higher mucus production than old mice. In chronic asthmatic state induced by i.p. and IN (three times) injection, old mice exhibited more inflammatory cells, specifically eosinophils, and mucus production than young mice. Our findings suggest that age and exposure duration are critical factors in different manifestations of asthma. Thus, they should be overarchingly considered in drug development for asthma.

Key Words: House dust mite, Asthma, Age, inflammation, Mucus

Asthma is a representative lung allergy due to allergens. It is characterized by meaningful clinical features such as infiltration of inflammatory cells, bronchoconstriction and mucus hypersecretion of goblet cells (Holgate, 2008; Hong et al., 2021; Lee, 2023). House dust mite (HDM) is a main allergen inducing asthma, allergic dermatitis, and allergic rhinitis (Kim and Lee, 2016; Kim, 2023). Most subjects with asthma have HDM-sensitive IgE. In this study, administration with HDM was used for inducing asthma in C57BL6/J mice. Acute and chronic asthma were induced by intraperitoneal (*i.p.*) and intranasal (IN) injection (three times, once per week), respectively, as described in a previous paper (Hong et al., 2021). Young (6 weeks) and old (12 months) mice were used for investigating age-dependent effect of HDM. All animal experiments used in this study were under a protocol approved by the Institutional Anima Care and Use Committee of the Eulji University (EUIACUC21-24). For evaluating the infiltration or movement of total cells, neutrophils and eosinophils, bronchoalveolar lavage fluid (BALF) was collected by lung lavage via the trachea with PBS. The BALF were centrifuged, and the cells in the BALF were resuspended in 100 μL of PBS. The cells were counted after they are stained with a Diff-Quick Kit (Sysmex Corporation, Kobe, Japan). First, we found that infiltration of total cells and eosinophils and mucus production increased in acute asthmatic mice (Fig. 1). Young mice exhibited more

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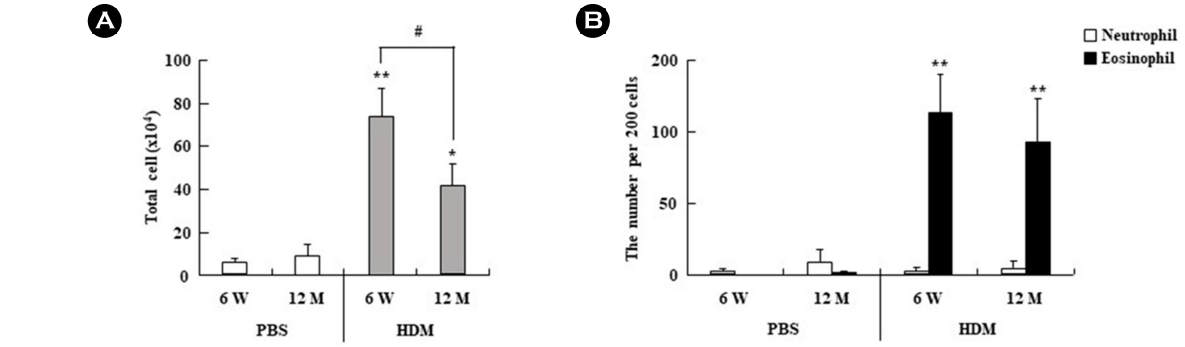


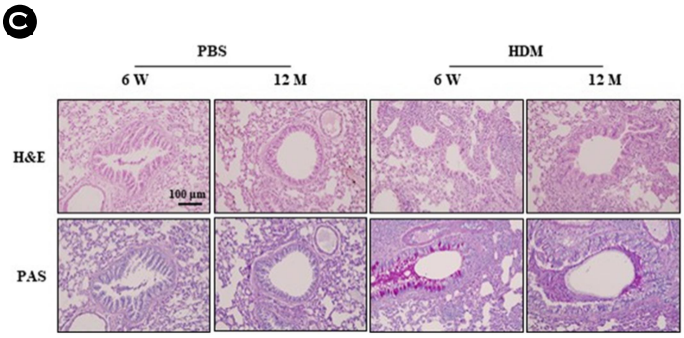
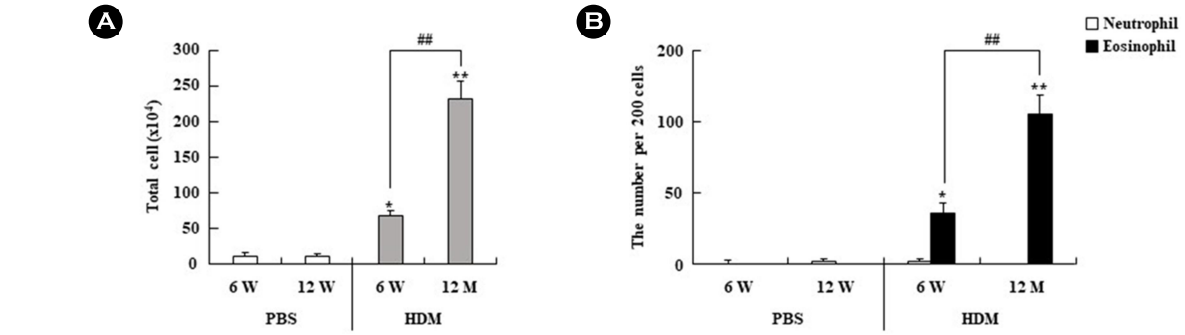


Fig. 1. Acute HDM administration induces higher eosinophil infiltration and mucin secretion in young mice than those in old mice. (A, B) Total cell counts (A) and differential counts (B) in BALF of 6 week and 12 month-aged C57BL6/J mice after i.p. and IN administration of HDM for 2 weeks with a week interval. (C) Lung tissues were separated from the mice and were stained with H&E and PAS. Magnification, 100 μm. Data are presented as the mean ± S.D. *$P < 0.05$ and **$P < 0.01$ indicate significant differences between the PBS-treated group and the HDM-treated group. #$P < 0.05$ indicates a significant difference between the 6 week-aged group and the 12 month-aged groups.



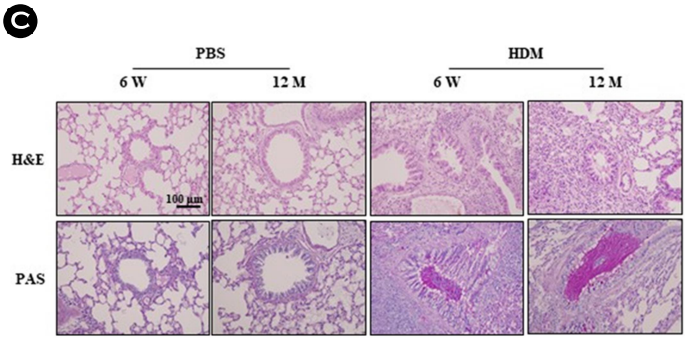


Fig. 2. Persistent HDM stimulation induces higher eosinophils infiltration and mucin production in old mice than those in young mice. (A, B) Total cell counts (A) and differential counts (B) in BALF of 6 week and 12 month-aged C57BL6/J mice after i.p. (one time) and IN (three times, once per week) administration of HDM for 4 weeks with a week interval. (C) Lung tissues were separated from the mice and were stained with H&E and PAS. Magnification, 100 μm. Data are presented as the mean ± S.D. *$P < 0.05$ and **$P < 0.01$ indicate significant differences between the PBS-treated group and the HDM-treated group. ##$P < 0.01$ indicates a significant difference between the 6 week-aged group and the 12 month-aged groups.

total cells and eosinophils in bronchoalveolar lavage fluid (BALF) and mucus secretion in lung tissues than old mice. Second, old mice exhibited more eosinophil movement and mucus production than young mice after chronic exposure to HDM (Fig. 2). There was no difference in alteration of neutrophils between young and old mice with both acute and chronic status of asthma (Figs. 1 and 2). Aging can decrease the physiologic function of the lung and alter the operation of the immune system related to hypersensitivity (Bullone and Lavoie, 2017; Busse et al., 2017). Age-related alterations can affect clinical features of asthma through complex and unknown mechanisms. After acute administration of HDM, eosinophils and neutrophils in old mice are increased compared to those in young mice (Brandenberger et al., 2014). In an ovalbumin-induced asthmatic mouse model, numbers of total cells and eosinophils in BALF of old mice are higher than young mice. Also, IL-4 and IL-5 decreased and IL-17 increased, triggering infiltration of neutrophils in old mice, in contrast to young mice (Kang, 2023). However, our results showed that young mice exhibited higher total cells and eosinophils than old mice in acute induction of asthma (Figs. 1A and B). Aging does not affect neutrophil infiltration. Surprisingly, persistent administration of HDM induced contrary results to acute administration (Fig. 2). Results based on Fig. 2 are similar to data from other papers besides neutrophils alteration (Kang et al., 2013; Busse et al., 2007). For mice with acute asthma, mucus production in young mice was higher than that in old mice. However, for mice with chronic asthma, mucus production in young mice was lower than that in old mice. The relationship between the increase of eosinophils and mucus secretion is consistent regardless aging. Increase of mucus secretion is related to hyperplasia of goblet cells (Raby et al., 2023). We underscore that acute and chronic sensitization of allergen including HDM is very important for studying asthma and aging (Del et al., 2020). In addition, asthma severity may be studied in the field of allergy. Researchers in the field of asthma have tried to clarify asthma's underlying immune mechanism because it is a heterogeneous disease (Habib et al., 2022). Phenotype and endotype are considered in the classification of asthma (Gans and Gavrilove, 2020). Although our findings are original, they are limited. Further study is needed to unveil the alteration of Th2 and Th17 cytokines, hyperresponsiveness to methacholine and T cell subsets in phenotype and endotype of asthma, depending on age and acute or chronic state.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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