



Anti-inflammatory and anti-asthmatic effects of resveratrol, a polyphenolic stilbene, in a mouse model of allergic asthma

Meeyoung Lee, Soyoung Kim, Ok-Kyoung Kwon, Sei-Ryang Oh, Hyeong-Kyu Lee, Kyungseop Ahn *

Natural Medicine Research Center, Korea Research Institute of Bioscience and Biotechnology, P.O. Box 115, Yuseong, Daejeon 305-600, Korea

ARTICLE INFO

Article history:

Received 11 September 2008

Received in revised form 29 December 2008

Accepted 5 January 2009

Keywords:

Asthma

Resveratrol

Airway hyperresponsiveness

Eosinophilia

Cytokine

ABSTRACT

Asthma is an inflammatory disease of the airways, and the current focus in managing asthma is the control of inflammation. Resveratrol (3,4,5-trihydroxystilbene) is a polyphenolic stilbene found in the skins of red fruits, including grapes, that may be responsible for some of the health benefits ascribed to consumption of red wine. We investigated the suppressive effects of resveratrol on asthmatic parameters such as cytokine release, eosinophilia, airway hyperresponsiveness, and mucus hypersecretion, in an OVA-induced allergic mouse model of asthma. Resveratrol significantly inhibited increases in T-helper-2-type cytokines such as IL-4 and IL-5 in plasma and bronchoalveolar lavage fluid (BALF), and also effectively suppressed airway hyperresponsiveness, eosinophilia, and mucus hypersecretion, in the asthmatic mouse model. The efficacy of resveratrol was similar to that of dexamethasone, a glucocorticoid used as a positive control. These results suggest that resveratrol may have applications in the treatment of bronchial asthma.

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1. Introduction

Asthma is an inflammatory disease of the lungs characterized by increased infiltration of leukocytes, especially eosinophils, into the airways, and reduced respiratory function. The inflammation leads to bronchoconstriction, increased airway hyperresponsiveness (AHR), and mucus production [1].

T-helper-2 (Th2) cytokine responses mediated by increases in IL-4, IL-5, IL-9, and IL-13, produced by T-cells, mast cells, and eosinophils, are prominently associated with asthma pathophysiology [2]. Allergen exposure in the airway produces a Th2-dominated response by recruiting and activating inflammatory cells including eosinophils, and increases the levels of IL-4, IL-13, and IL-5 [3]. IL-4 upregulates the expression of endothelial vascular cell adhesion molecule-1 (VCAM-1), which interacts with very late antigen-4 (VLA-4) to promote the recruitment of eosinophils [4]. IL-4 also causes class switching in B cells, resulting in the synthesis of IgE, which is involved in mast cell degranulation by crosslinking with IgE receptors [5]. Resveratrol (*trans*-3,4,5-trihydroxystilbene), a natural polyphenol, is found in various fruits and vegetables and is abundant in grapes [6]. Root extracts of the weed *Polygonum cuspidatum*, an important constituent of Japanese and Chinese folk medicine, is also an ample source of resveratrol [7]. In plants, resveratrol functions as a phytoalexin that protects against fungal infections [6,8]. Earlier studies documented that resveratrol exhibits a wide range of biological and pharmacological activities, such as anticarcinogenesis, cardiovascular protection,

and anti-inflammatory effects [9,10]. Also, several studies within the last few years have confirmed that resveratrol exhibits cardioprotective and chemopreventive effects [11,12]. How exactly resveratrol exerts cardioprotective effects is not understood, but the results have been ascribed to the ability of resveratrol to block platelet aggregation [13,14], to inhibit oxidation of low density lipoprotein [15,16], and to induce NO production [17]. More recently, the anti-inflammatory effects of resveratrol have been associated with inhibition of the transcription factor NF- κ B [18], possibly mediated by inhibition of I κ B kinase [19]. NF- κ B activation is required for the expression of many inflammatory proteins, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8, COX-2, and inducible nitric oxide synthase (iNOS) [20,21]. Therefore, inhibition of NF- κ B might reduce the expression of inflammatory genes and is one mechanism whereby anti-inflammatory glucocorticosteroids might exert their effects [22]. Resveratrol has been demonstrated to suppress macrophage activation, which would account for the anti-inflammatory effect of the compound [23,24]. Therefore, in this study, we used a bronchial asthma model to examine the anti-allergic and anti-inflammatory effects of resveratrol in an ovalbumin (OVA)-induced asthmatic mouse model.

2. Materials and methods

2.1. Animals

Specific pathogen-free female BALB/c mice, aged 6–8 weeks, which were routinely screened serologically for relevant respiratory pathogens, were purchased from the Orient Co. (Seoul, Korea). The mice were maintained in an animal facility under standard laboratory

* Corresponding author. Tel: +82 42 860 4482; fax: +82 42 860 4309.
E-mail address: ksahn@kribb.re.kr (K. Ahn).

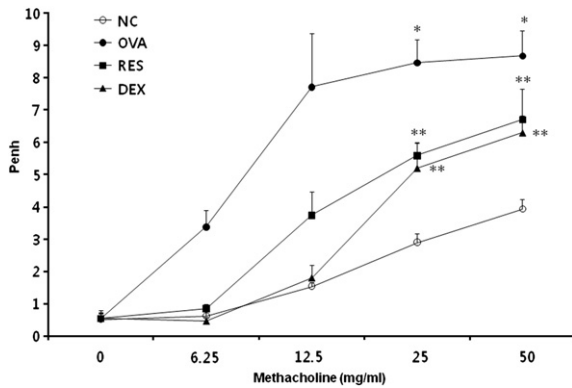


Fig. 1. Effect of resveratrol on airway hyperresponsiveness (AHR). AHR was measured using plethysmography 24 h after the last ovalbumin (OVA) challenge, in mice given increments of methacholine (6.25–50 mg/mL). NC, normal control (PBS only); OVA, OVA sensitized/challenged mice; RES, resveratrol (30 mg/kg)+OVA sensitized/challenged mice; DEX, dexamethasone (3 mg/kg)+OVA sensitized/challenged mice. Values are expressed as means $\pm$ SEMs. *Significant difference from NC and **significant difference from OVA, $P < 0.05$.

conditions for 1 week prior to experiments, and were provided with water and standard chow *ad libitum*. All experimental procedures were carried out in accordance with the NIH Guidelines for the Care and Use of Laboratory animals, and all animal handling followed the dictates of the National Animal Welfare Law of Korea.

2.2. Sensitization and airway challenge

Mice were used in groups ($n=5$ or $n=6$), and received the following treatments: (1) sham-sensitization plus challenge with phosphate-buffered saline (PBS; ipNeb); (2) sensitization plus challenge with OVA (Sigma A5503; Sigma, St. Louis, MO) (ipNeb); (3) sensitization with OVA (i.p.) plus challenge with OVA (Neb) and drugs (resveratrol [Sigma, St. Louis, MO, USA; 30 mg/kg] or dexamethasone [Sigma, St. Louis, MO, USA; 4 mg/kg, p.o.]). Briefly, mice were sensitized by intraperitoneal injection of 20 μ g OVA, which was emulsified in 2 mg aluminum hydroxide in 100 μ L of PBS buffer (pH 7.4), on days 0 and 14. The mice were challenged through the airways with OVA (1%, w/v, in PBS) for 20 min using an ultrasonic nebulizer (NE-U12; Omron Corp., Tokyo, Japan) on days 28, 29, and 30 after the initial sensitization. Mice were sacrificed 48 h after the last challenge (day 32) to characterize the suppression effects of resveratrol on the airways of allergic asthma animals.

2.3. Measurement of airway hyperresponsiveness (AHR)

Twenty-four hours after the final aerosol challenge, AHR was assessed in conscious and unrestrained mice by means of whole-body plethysmography (OCP3000 instrument; Allmedicus, Korea). Each mouse was placed in a plastic chamber and exposed to aerosolized PBS, which was followed by increasing concentrations of aerosolized methacholine solutions (6.25, 12.5, 25, 50 mg/mL; Sigma) in PBS, with 3 min at each exposure. Bronchoconstriction was recorded for an additional 5 min after each dose of methacholine. The highest Penh value obtained during each methacholine challenge was expressed as a proportion of the basal Penh value seen in response to PBS challenge.

2.4. Inflammatory cell counts in bronchoalveolar lavage fluid (BALF)

Mice were sacrificed with an overdose of 50 mg/kg of pentobarbital (Sigma P3761) 48 h after the last challenge, and tracheotomies were performed. After ice-cold PBS (0.5 mL) was instilled into the lungs, bronchoalveolar lavage fluid (BALF) was obtained by two aspirations (total 1.2 mL) via tracheal cannulation [25]. The BALF was centrifuged and supernatants were collected and stored at -70°C prior to use. Total inflammatory cell numbers were assessed by counting cells in at least

five squares of a hemocytometer, after exclusion of dead cells staining with trypan blue [26]. One hundred microliters of BALF was loaded onto a slide and centrifuged (cytospin instrument; Hanil Science Industrial, Korea) (200 $\times$ g, 4°C , 10 min) to fix the cells onto the slide using a cytospin machine (Hanil Science Industrial, Korea). Cell pellets was suspended in 0.5 mL of PBS, and 100 μ L of each solution was spun onto a slide. After slides were dried, cells were fixed and stained using Diff-Quik® Stain reagents (B4132-1A; Dade Behring Inc., Deerfield, IL) according to the manufacturer's instructions.

2.5. Measurement of total IgE and OVA-specific antibodies in serum

Serum was collected and stored at -70°C after centrifugation. Total IgE and OVA-specific IgE and IgG_{2a} were measured by ELISA. For the determination of total IgE and OVA-specific IgE and IgG_{2a} antibodies, microtiter plates were coated with 100 μ L/well IgE (2 μ g/mL; Serotec, Oxford, UK) or OVA (10 μ g/mL; Sigma) in PBST. Antibodies was detected using isotype-specific secondary antibodies (anti-mouse IgE; Serotec, or anti-mouse IgG_{2a} conjugated to HRP; Bethyl Laboratories, TX), in serum samples. After washing another four times, 200 μ L of *o*-phenylenediamine dihydrochloride (Sigma) was added to each well. The plate was incubated for 10 min in the dark and absorbance measured at 450 nm. Total IgE concentrations were calculated from a standard curve generated using recombinant IgE 250 ng/mL (Serotec, Oxford, UK).

2.6. Measurement of Th2 cytokines in BALF

Enzyme-linked immunosorbent assays (ELISAs) were performed according to the manufacturer's directions. Interleukin-4 (IL-4) and IL-5 contained in BALF were measured using a specific mouse IL-4 and IL-5 ELISA kit (R&D Systems, Minneapolis, MN).

2.7. Lung tissue histopathology

After BALF was obtained, the lung tissue was fixed in 10% (v/v) neutral buffered formalin for 24 h. Lung tissue was embedded in paraffin, cut into sections of 4 μ m thickness, stained with H & E solution (hematoxylin, Sigma MHS-16; and eosin, Sigma HT110-1-32), and with periodic acid-Schiff (PAS) stain (IMEB Inc., San Marcos, CA) to measure mucus production. Tissue was subsequently mounted and coverslipped using Dako-mounting medium (Dakocytomation,

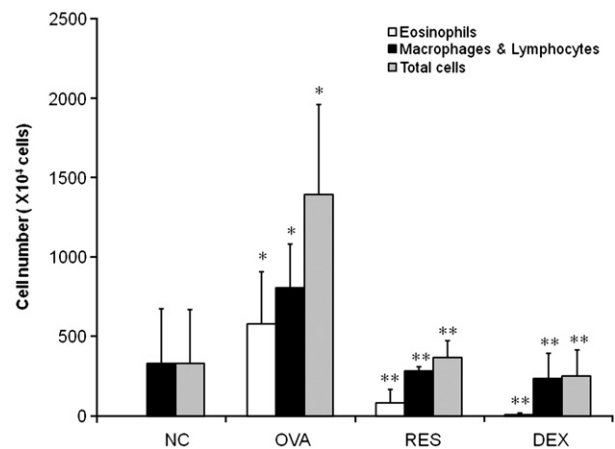


Fig. 2. Effect of resveratrol on the recruitment of inflammatory cells in bronchoalveolar lavage fluid (BALF) of mice 48 h after the last OVA challenge. Cells were isolated by cytospinning and stained with Diff-Quik®. Cell numbers was assessed by counting cells directly under a light microscope in at least five squares of a hemocytometer, after excluding dead cells staining with trypan blue. NC, normal control mice (PBS only); OVA, OVA-sensitized/challenged mice; RES, resveratrol (30 mg/kg)+OVA-sensitized/challenged mice; DEX, dexamethasone (3 mg/kg)+OVA-sensitized/challenged mice. Values are expressed as means $\pm$ SEMs ($n=6$ /group). *Significant difference from NC, $P < 0.001$, and **significant difference from OVA, $P < 0.005$.

Denmark, CA). The degree of airway inflammatory cell infiltration was scored in double-blind screening by two independent investigators [27]. The peri-bronchiole and peri-vascular inflammation was evaluated by using a scoring of 0–5, 0, no cells; 1, a few cells; 2, a ring of cells 1 cell-layer deep; 3, a ring of cells 2–4 cells deep; 4, a ring of cells; 5, cells deep. Goblet-cell hyperplasia in the airway epithelium was quantified based on a five-point system: 0, no goblet cells; 1, <25% of the epithelium; 2, 25–50% of the epithelium; 3, 50–75% of the epithelium; 4, >75% of the epithelium. For each mouse, five airway sections that were randomly distributed throughout the left lung were analysed, and their average scores were calculated. Quantitative analysis of mucus production was performed using an image analyzer (Leica Microsystem Imaging solution Ltd., Cambridge, UK).

2.8. Image capture and photomicrographs

Photomicrographs were captured with a Photometric Quantix digital camera running a Windows program and montages were

assembled in Adobe Photoshop 7.0. The images were then cropped and corrected for brightness and contrast, but were not otherwise manipulated.

2.9. Statistical analysis

Data are expressed as means±standard errors of the means (SEMs). Statistical significance was determined using Student's two-tailed *t*-test to compare independent means, employing Microsoft Excel. The critical level for significance was set at $P<0.05$.

3. Results

3.1. Effect of resveratrol on AHR

AHR was evaluated by calculation of Penh values (enhanced pauses) 24 h after the final OVA challenge. The Penh value of the OVA-treated group was significantly higher than that of the PBS control

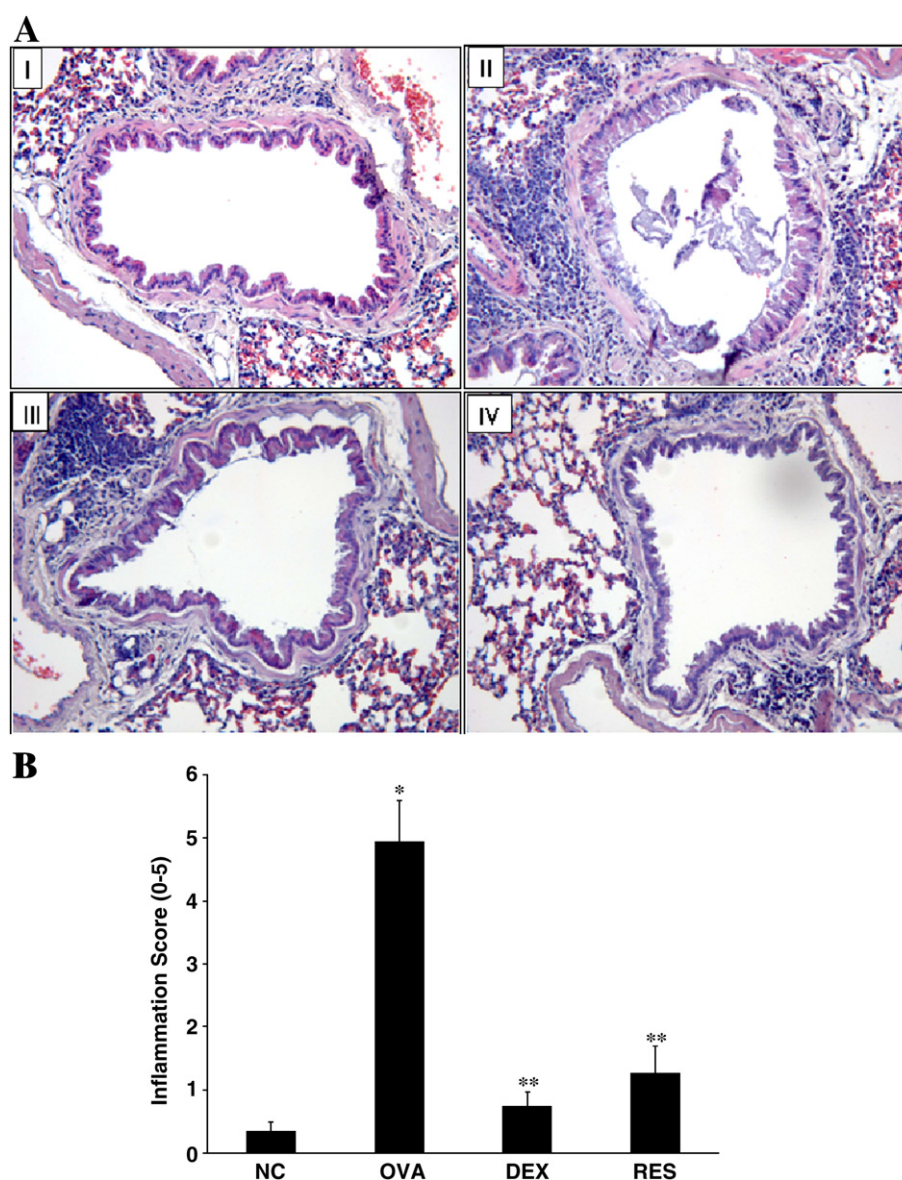


Fig. 3. Effects of resveratrol on the recruitment of leukocytes in lung tissue. (A) Histological examination of lung tissue was performed 48 h after the last OVA challenge. Lung tissues were fixed, sectioned at 4 μ m thickness, and stained with H&E solution (magnification $\times 200$). (B) Scoring of the extent of inflammation by quantitative analysis of inflammatory-cell infiltration in lung sections was based on the method of Myou et al. [27]. I and NC, normal control mice (PBS only); II and OVA, OVA-sensitized/challenged mice; III and RES, resveratrol (30 mg/kg)+OVA-sensitized/challenged mice; IV and DEX, dexamethasone (3 mg/kg)+OVA-sensitized/challenged mice. *Significant difference from NC, $P<0.005$, and **significant difference from OVA, $P<0.05$.

group ($P<0.05$) at any concentration between 6.25–50.0 mg/mL of methacholine. In the resveratrol+OVA-challenged group, the Penh value was significantly reduced compared with that of the OVA-treated group ($P<0.05$). The positive control, mice given dexamethasone (widely used as an anti-asthmatic drug), showed a similar decrease of AHR with resveratrol (Fig. 1).

3.2. Effect of resveratrol on OVA-induced eosinophilia in BALF

To evaluate the suppression by resveratrol of eosinophilia in OVA-challenged mice, cells recruited to the BALF were counted 48 h after the last challenge. OVA caused a marked influx of leucocytes into the BALF in a PBS control group. Total cells were $15.3\pm3.4\times10^5$ cells/mouse ($P<0.001$) compared with the PBS-treated control ($2.1\pm0.9\times10^5$ cells/mouse). Eosinophils were found to be less than 1% of total cells in PBS-treated mice. However, eosinophil levels dramatically increased to form more than 86.3% of total leukocytes, in the BALF of OVA-challenged mice. In resveratrol-treated mice, cell

migration was significantly attenuated. A $76.7\pm13.1\%$ decrease in total cells ($P<0.005$) and an 89.8% drop in eosinophils ($P<0.001$) was seen, compared to the OVA-treated control group. A positive drug control, dexamethasone, showed a similar suppressive effect on leukocyte influx into the BALF (Fig. 2). There was an $84.6\pm12.1\%$ decrease in total cells ($P<0.005$) and a $97.6\pm11.1\%$ decrease in eosinophils ($P<0.005$).

3.3. Effect of resveratrol on OVA-induced eosinophilia in lung tissue

To estimate the anti-inflammatory or anti-remodeling effects of resveratrol, lung tissues were collected 48 h after the last OVA challenge. In OVA-challenged mice, leukocytes were found to have infiltrated into the peribronchiole and perivascular connective tissue; most leukocytes were eosinophils (Fig. 3; and OVA, $P<0.05$). In the resveratrol+OVA-challenged mice, the infiltration of eosinophil-rich leukocytes was significantly attenuated compared to what was seen in OVA-treated mice (Fig. 3; and RES, $P<0.05$).

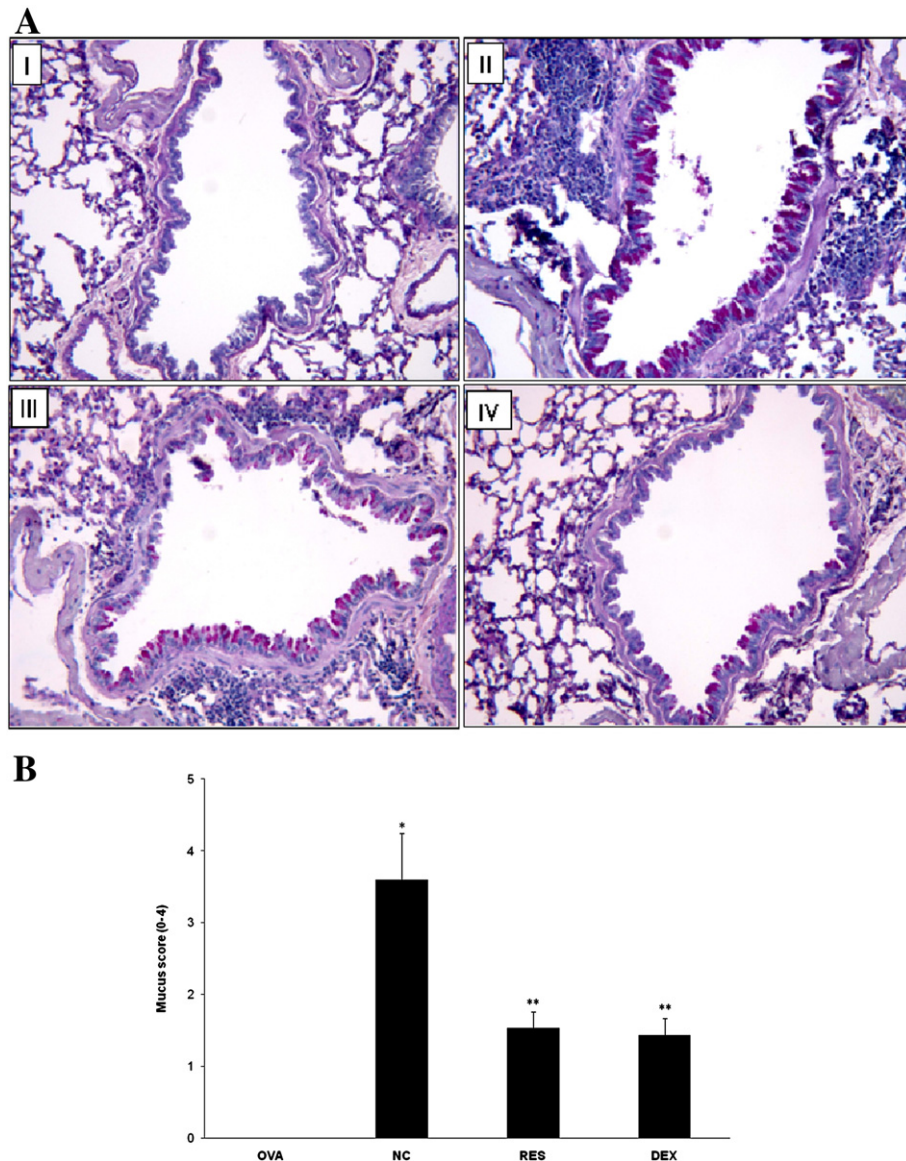


Fig. 4. Effects of resveratrol on mucus production. (A) Histological examination of mucus secretion in lung tissue was measured 48 h after the last OVA challenge in mice. Lung tissues were fixed, sectioned at 4 μ m thickness, and stained with periodic acid Schiff (PAS) reagent to assess mucus production. (magnification $\times 200$). (B) Scoring of mucus production in lung sections was based on the method of Myou et al. [27]. I and NC, normal control mice (PBS only); II and OVA, OVA-sensitized/challenged mice; III and RES, resveratrol (30 mg/kg) + OVA-sensitized/challenged mice, IV and DEX, dexamethasone (3 mg/kg) + OVA-sensitized/challenged mice; *Significant difference from NC, $P<0.005$, and **significant difference from OVA, $P<0.05$.

3.4. Effect of resveratrol on airway goblet cell hyperplasia and mucus production

Mucus hypersecretion is a characteristic of airway remodeling. To evaluate the possible suppression by resveratrol of mucus overproduction caused by goblet-cell hyperplasia, we stained lung sections with Periodic acid Schiff (PAS), and scored percentages of stained areas in each experimental group. In OVA-treated mice, mucus overproduction was clearly observed as a violet color in the bronchial airways, compared with PBS-treated mice. In contrast, mucus was markedly diminished in the resveratrol+OVA-challenged mice (Fig. 4A). The mucus area was scored as 3.60 ± 0.64 in the OVA-treated mice compared with PBS-treated mice ($P < 0.05$), and the area was significantly decreased to 1.43 ± 0.23 in the resveratrol+OVA-treated mice ($P < 0.05$), which was even lower than that of the positive control, dexamethasone+OVA-treated animals (1.53 ± 0.24 , $P < 0.05$) (Fig. 4B). This shows that resveratrol significantly reduced goblet-cell hyperplasia and the mucus hypersecretion of the airway remodeling process.

3.5. Effect of resveratrol on the release of total IgE and OVA-specific IgE into serum

Levels of total serum IgE and OVA-specific serum IgE were determined by ELISA in each experimental group, 48 h after the last OVA challenge. The total IgE and OVA-specific IgE levels in serum were

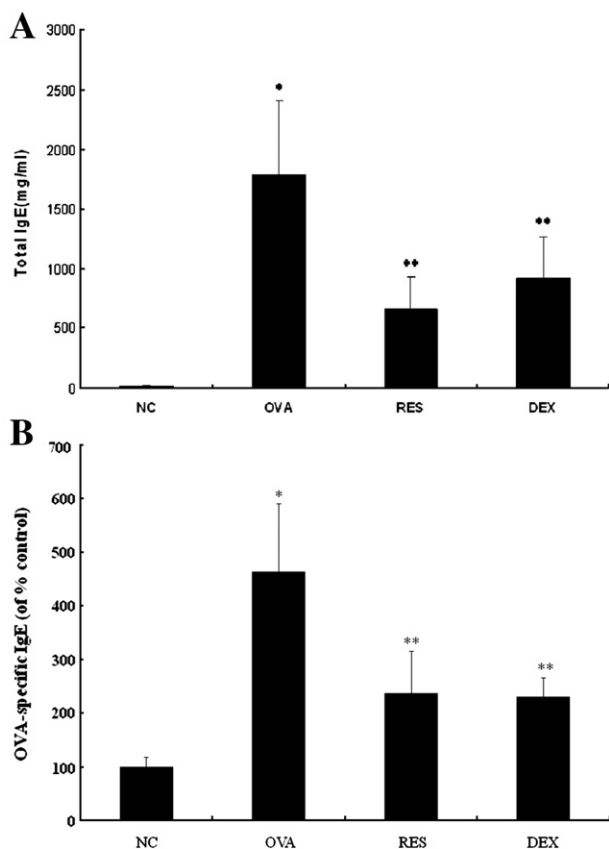


Fig. 5. Effect of resveratrol on total IgE and OVA-specific IgE levels in BALF. BALF was collected 48 h after the last ovalbumin (OVA) challenge of mice. Each sample was analyzed by ELISA ($n=5$ or $n=6$ /group). Upper: Total IgE level in BALF; lower: OVA-specific IgE level in BALF. NC, normal control mice (PBS only); OVA, OVA-sensitized/challenged mice; RES, resveratrol (30 mg/kg)+OVA-sensitized/challenged mice; Dex, dexamethasone (3 mg/kg)+OVA-sensitized/challenged mice. Values are expressed as means $\pm$ SEMs ($n=5$ or $n=6$ /group). *Significant difference from NC, $P < 0.005$, and **significant difference from OVA, $P < 0.05$.

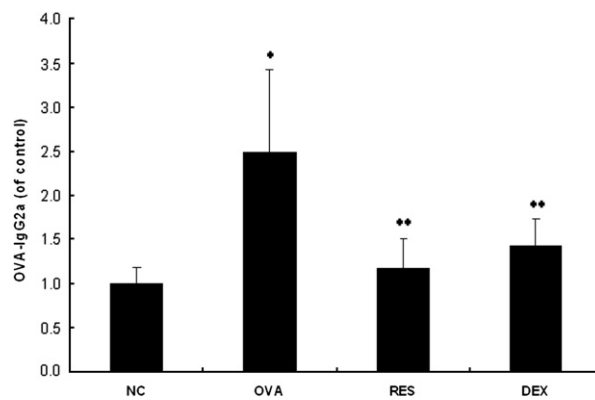


Fig. 6. Effect of resveratrol on OVA-specific IgG and OVA-specific IgG2a levels in BALF. BALF was collected 48 h after the last ovalbumin (OVA) challenge of mice. Each sample was analyzed by ELISA ($n=5$ or $n=6$). Upper: OVA-specific IgG levels in BALF; lower: OVA-specific IgG2a levels in BALF. NC, normal control mice (PBS only); OVA, OVA-sensitized/challenged mice; RES, resveratrol (30 mg/kg)+OVA-sensitized/challenged mice; Dex, dexamethasone (3 mg/kg)+OVA-sensitized/challenged mice. Values are expressed as means $\pm$ SEMs ($n=5$ or $n=6$ /group). *Significant difference from NC, $P < 0.005$, and **significant difference from OVA, $P < 0.05$.

dramatically elevated in OVA-treated mice compared with PBS-treated mice. Treatment with resveratrol reduced the total IgE and OVA-specific IgE levels compared with the OVA-challenged group (Total IgE: 1793 ± 614 mg/mL vs 662.42 ± 272.6 mg/mL; OVA-specific IgE: 463.12 ± 127.12 [of control] vs 232.02 ± 79 [of control]; $P < 0.05$; control and test, respectively) (Fig. 5).

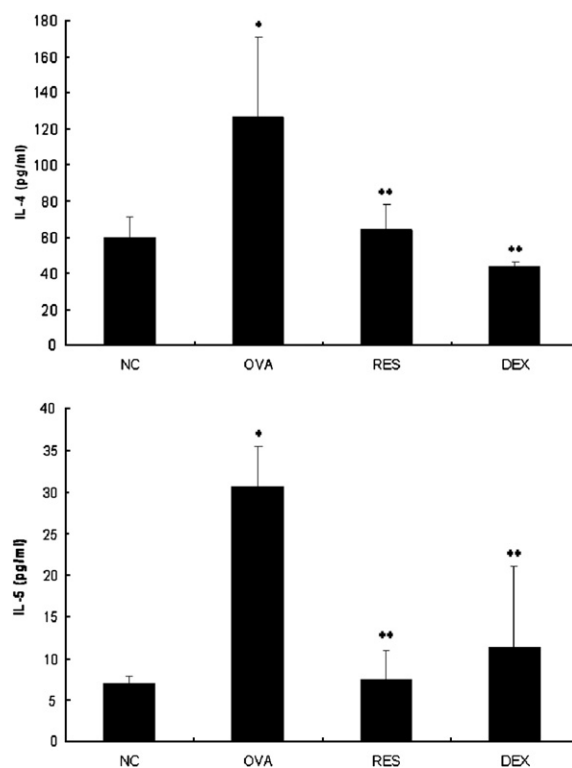


Fig. 7. Effect of resveratrol on cytokine levels in BALF. BALF was collected 48 h after the last ovalbumin (OVA) challenge. Each sample was analyzed using ELISA ($n=5$ or $n=6$ /group). (A) interleukin (IL)-4 level in BALF; (B) IL-5 level in BALF. NC, normal control mice (PBS only); OVA, OVA-sensitized/challenged mice; RES, resveratrol (30 mg/kg)+OVA-sensitized/challenged mice; Dex, dexamethasone (3 mg/kg)+OVA-sensitized/challenged mice. Values are expressed as means $\pm$ SEMs ($n=5$ or $n=6$ /group). *Significant difference from NC, $P < 0.005$, and **significant difference from OVA, $P < 0.05$.

3.6. Effect of resveratrol on the release of OVA-specific IgG and IgG2a into serum

Serum levels of OVA-specific IgG and IgG2a were determined by ELISA in each experimental group, 48 h after the last challenge. The OVA-specific IgG and IgG2a levels in serum were dramatically elevated in OVA-treated mice compared with PBS-treated mice. Treatment with resveratrol reduced OVA-specific IgG2a (not IgG) levels compared to those seen in the OVA-challenged group (OVA-specific IgG2a: 2.49 ± 0.93 -fold [of control] vs. 1.18 ± 0.31 [of control], [IgG]; $P < 0.05$) (Fig. 6).

3.7. Effect of resveratrol on cytokine levels

To determine the effect of resveratrol on cytokine release in OVA-induced asthmatic mice, the levels of cytokines (IL-4 and IL-5) in BALF were measured by ELISA 48 h after the last challenge. OVA challenge induced a significant elevation of cytokines to 102 ± 17.3 pg/mL (IL-4) and 30.6 ± 4.8 pg/mL (IL-5) in BALF, compared with control BALF (IL-4, < 60 pg/mL; IL-5, < 7 pg/mL). In the resveratrol-treated group, cytokine elevation was significantly suppressed; there was a 64 ± 14 pg/mL decrease in IL-4 ($P < 0.05$) and a 4.6 ± 1 pg/mL drop in IL-5 ($P < 0.005$), compared to the OVA-challenged group. Dexamethasone also caused a significant reduction in both IL-4 (44 ± 2.4 pg/mL decrease, $P < 0.05$) and IL-5 (11.4 ± 9.8 pg/mL decrease, $P < 0.05$) from control values. These results demonstrate that resveratrol reduced IL-4 and IL-5 concentrations in BALF of asthmatic mice, as did dexamethasone (Fig. 7).

4. Discussion

Asthma is an inflammatory disease of the lungs characterized by increased infiltration of leukocytes, especially eosinophils, into the airways, and reduced respiratory function. The inflammation leads to bronchoconstriction, increased AHR, and mucus production [28]. In asthmatic patients, numerous eosinophils and T-lymphocytes infiltrate peribronchial tissue. However, asthma is a complex syndrome with many clinical phenotypes [29]. The resolution of acute inflammation is an active process that is essential for the establishment of appropriate host responses, tissue protection, and the return to homeostasis [30–32]. It is well known that Th-lymphocytes play a key role in the regulation of immune and inflammatory reactions through the release of cytokines [33–35].

Resveratrol has been detected in trees, in a few flowering plants, in peanuts, and in grapevines. Numerous *in vitro* studies have described different biological effects of resveratrol (for review, see reference [36]). The major properties of interest are the antioxidative, anti-inflammatory, and estrogenic effects, as well as anticancer and chemopreventative activities [37,38]. Recently, resveratrol has been suggested to have many properties that could be beneficial in the treatment of several chronic inflammatory diseases such as chronic obstructive pulmonary disease (COPD) and arthritis [39,40]. Although it was earlier reported that resveratrol reduced inflammatory mediators in COPD patients [39], *in vivo* demonstration of any anti-allergic or anti-asthmatic property of resveratrol was lacking. Here we demonstrate such properties, for the first time, using an OVA-induced mouse model of allergic asthma.

Before investigating the effects of resveratrol (30 mg/kg) in a mouse model of allergic asthma, we studied preliminarily the dose effects of resveratrol (20, 30 and 50 mg/kg) on IgE, IgG, and IgG2a in serum to confirm the optimal dosages of resveratrol (data not shown). We used 30 mg/kg (similar to 50 mg/kg) of resveratrol because that dosage was most effective. In the present study we show that resveratrol (30 mg/kg) markedly reduced the AHR response to methacholine; significantly inhibited increases in total inflammatory cell counts and eosinophil counts in BALF induced by ovalbumin; reduced the levels of total IgE, OVA-specific IgE, IgG2a, IL-4, and IL-5 in

serum and BALF; and substantially inhibited both OVA-induced eosinophilia in lung tissue and mucus hypersecretion by airway goblet cells.

In most cases, AHR is strongly associated with airway inflammation [41,42]. AHR is a measure of the bronchial constriction commonly found in asthmatics. Our data show that resveratrol inhibited OVA-induced AHR caused by inhaled methacholine. IL-5 is a specific stimulator of eosinophil activation and is synthesized by Th2 lymphocytes, mast cells, and eosinophils [43]. It has been established that IL-5-mediated eosinophilia contributes to AHR by generating cytotoxic products, such as major basic protein (MBP), eosinophilic cationic protein (ECP), and other lipid mediators, including platelet activated factor (PAF) and cysteinyl-leukotrienes, which lead to tissue damage [44]. Th2 lymphocytes play an important role in the initiation and progression of allergic diseases, including asthma, by releasing IL-4, IL-5, and IL-13 [45]. These Th2 cytokines induce inflammatory responses, such as airway infiltration and eosinophil activation, IgE production, and mucus secretion [46–48]. In the knockout murine model, these cytokines have been implicated in the processes of sensitization and allergic responsiveness, causing increases in IgE levels [49], and eosinophilia into the airways [50]. The presence of increased numbers of BALF eosinophils is a hallmark of asthma. We found that, compared with PBS-treated mice, resveratrol-treated mice had significantly reduced lung eosinophilia in BALF and lung tissue. This effect of resveratrol treatment may result from a decrease in the levels of Th2 cytokines responsible for eosinophil recruitment into the lung in asthma. IgE, together with IgG1, has been closely associated with Th2-type responses, whereas IgG2a has been allied to Th1-type responses. Oral administration of resveratrol to OVA-sensitized/challenged mice significantly decreased serum IgE levels and IgG2a levels, but had no effect on overall IgG levels. Our present results show that oral administration of resveratrol inhibited IgE production and increased IgG2a levels in serum. These effects could be related to the induction of Th1-type IL-12 and IFN- γ production, and inhibition of Th2-related IL-5 and IL-13 synthesis. In this study, resveratrol significantly reduced the levels of total IgE, OVA-specific IgE, IgG2a, IL-4, and IL-5 in plasma and BALF in an OVA-induced asthmatic mouse model. These results provide further evidence that oral administration of resveratrol is suitable for treatment of allergic diseases such as asthma.

Acknowledgements

This work was supported by grants from the Ministry of Education, Science and Technology (PDM0500839; KGM2110812), Republic of Korea.

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