



Effects of oral monosodium glutamate in mouse models of asthma

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ABSTRACT

The available evidence from numerous clinical studies has failed to demonstrate a clear and consistent relationship between monosodium glutamate (MSG) and asthma. The objective of this study was to investigate the effects of MSG on bronchial inflammation by measuring cytological, histological and functional changes in an ovalbumin-induced asthma mouse model. BALB/c mice with experimentally induced asthma were fed a diet containing 0.5% or 5% MSG the week before the first ovalbumin injection and for the subsequent 3-week period. MSG feeding did not affect pulmonary eosinophil infiltration, production of Th2 cytokines, circulating IgE concentrations or airway hyperresponsiveness (induced by methacholine). Histological observations did not reveal pulmonary inflammation, including secondary changes, in the asthmatic mice. An oral gavage challenge with an MSG solution (0.5% or 5%, w/w) did not exert any acute effects on lung inflammation or airway hyperresponsiveness in the asthmatic mice. The results of this study suggest that MSG is not involved in the development of asthma or in acute asthmatic responses, and they support previous observations from well-designed clinical studies.

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1. Introduction

Since the discovery by Dr. Ikeda in 1908 that glutamate and/or its salts are the source of the savoury taste of traditional Japanese soup, monosodium glutamate (MSG), the sodium salt of glutamate, has been commonly used around the world in a wide range of foods to create a smooth, rich, and full-bodied flavor (Ikeda, 2002). Glutamate, one of the 20 standard amino acids that make up proteins, is also abundant in foods such as meat, cheese and tomato by nature and is responsible for their savoury taste (Kurihara and Kashiwayanagi, 2000). In recent years, it has been recognised that the taste of glutamate, i.e., “umami,” is one of the five basic tastes, along with sweet, bitter, salt, and sour (Kondoh et al., 2000).

While human beings sense free glutamate in foods as umami via taste receptors (Brand, 2000), foods contain another form of glutamate as protein constituent. Almost all dietary glutamate, both in free form and as protein constituent, is metabolized in the intestinal mucosa. Dietary glutamate is a major energy source and an important substrate for the synthesis of glutathione and other amino acids in the gut (Reeds et al., 2000). The average intake of native glutamate as protein constituent and in its free form has been estimated to be approximately 10 and 1 g/day, respectively, in European countries (Beyreuther et al., 2007). With respect to

added glutamate mostly in the form of MSG, the average intake ranges 0.3 to 0.5 g/day in European countries and 1.2 to 1.7 g/day in Asian countries (Beyreuther et al., 2007). These levels of added glutamate in addition to intake from its natural presence in food (background intake) are considered safe (Walker and Lupien, 2000; Beyreuther et al., 2007). More than 90 years of experience with MSG usage in food seasoning supports its safety; however, public concern about the role of food additives remains high (Simon, 2000).

Asthma is a chronic respiratory disorder characterized by airway inflammation, reversible airway obstruction, coughing spasms, and increased airway hyperresponsiveness to a variety of stimuli (Rodrigo et al., 2004). According to the National Health Interview Survey in the United States, the estimated prevalence of self-reported asthma was 5.4% in 1994, a 75% increase in recent decades. Epidemiological and experimental studies using animal models for asthma suggest that air pollution, especially in urban areas, is at least partially involved in this rapid increase in asthma prevalence (McCreanor et al., 2007). Although some reports indicate the possible involvement of food additives, including Food, Drug, and Cosmetic Act (FD&C) approved dyes, benzoate, and tartrazine in the cause of allergic hyperresponsiveness (Genton et al., 1985), many adverse reactions reported to additives were anecdotal or characterized by poorly controlled challenge procedures (Simon, 1986). Allen and Baker (1981), Allen et al. (1987) and Moneret-Vautrin (1987) reported a relationship between MSG intake and asthma; however, their studies lacked proper control groups. In subsequent studies by Schwartzstein et al. (1987),

Abbreviations: MSG, monosodium glutamate; BALF, bronchoalveolar lavage fluid; OVA, ovalbumin.

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Woods et al. (1998), and Woessner et al. (1999), which were performed under properly controlled conditions, no relation between asthma and MSG was noted. In these studies, MSG challenge of subjects with asthma failed to induce the signs or symptoms of asthma. However, the misapprehension that MSG intake can lead to an asthma attack has persisted (Woods et al., 1998). Although recent clinical studies have clearly shown no involvement of MSG intake in the development of asthma symptoms, data from a mechanistic perspective that support the absence of a relationship between MSG and asthma symptoms are lacking. Detailed analysis including evaluation of histological, cytological and functional changes also seems insufficient because of the lack of animal studies. Therefore, in the present study, we investigated the safety of MSG in a well-established animal model for asthma.

2. Materials and methods

2.1. Test substance

L-Glutamic acid monosodium salt monohydrate, CAS Number 6106-04-3, MSG (Ajinomoto Co., Inc. Tokyo, Japan) was supplied as a white crystalline powder and stored at room temperature. The quality of the test substance meets the standards of the Food Chemicals Codex (2010) (purity 98.5–101.5%, inorganic impurity $\leq$ 0.2%).

2.2. Animals and experimental design

The study received prior approval from Ajinomoto's Institutional Animal Care and Use Committee. Male Balb/c mice (Charles River Laboratories, Shizuoka, Japan) were maintained in controlled conditions: 12 h light (0700 to 1900) and 12 h dark at $23 \pm 1^\circ\text{C}$ and $60 \pm 10\%$ humidity. The animals were housed in plastic cages and had free access to tap water and purified diet based on the AIN-93G composition with some modifications, as reported previously (Toue et al., 2006).

The asthma model mice were prepared using ovalbumin (OVA) as an antigen, as reported by Duan et al. (2004). Briefly, mice aged 7 to 8 weeks and weighing 22.5 ± 1.1 g were injected intraperitoneally with 8 μg /mouse of OVA mixed with 2 mg of alum as an adjuvant (day 0) and boosted with same mixture on day 5. The mice were subsequently challenged with aerosolized OVA solution (1.5%, w/w) for 30 min on day 12, day 16, and day 20 to induce pulmonary allergy. Non-asthmatic control mice were treated similarly with vehicle. In a series of experiments, an experimental diet containing 0%, 0.5% or 5% (w/w) MSG was given to the mice during the week before the first immunization and during the subsequent 3-week period. The diets were stored at 4°C before use during the experiment. In another series of experiments, MSG was administered only on the last day of the study (day 21) via oral gavage after a 4-h fasting period. In these experiments, the animals were orally administered a 0%, 0.5% or 5% MSG solution prepared in 10 mM phosphate buffered saline (PBS, vehicle) at a dose of 15 ml/kg (corresponding to 75 or 750 mg/kg of MSG, respectively) 30 min before the assessment of airway responsiveness and the cytological analysis described below. An MSG solution was prepared before use. Dexamethasone (1 mg/kg, i.p.) was injected 3 times per week during the 3-week OVA sensitization period as a therapeutic control.

2.3. Airway Responsiveness

Airway responsiveness was measured in mice at 24 h after the final OVA challenge. Respiratory pressure curves were recorded by whole body plethysmography (Buxco Electronics, Inc., Osaka, Japan) in response to inhalation of aerosolized methacholine (Sigma–Aldrich) solution at concentrations of 3.125–12.5 mg/ml for 1 min, as described previously (Broide and Raz, 1999). Enhanced pause (Penh) was calculated from the chamber pressure–time wave as an indicator of airway obstruction. This measurement shows a strong correlation with airway resistance measured using standard procedures (Broide and Raz, 1999). Penh values were recorded for 10 min after each methacholine inhalation. Mean Penh values determined for the first 5 min after the end of nebulization were used as individual data.

2.4. Blood and bronchoalveolar lavage fluid collection

Blood and bronchoalveolar lavage fluid (BALF) were collected 24 h after the last challenge of aerosolized OVA. Blood was collected from the inferior vena cava under ether anesthesia, allowed to clot, and centrifuged to obtain serum samples. Following exsanguination, the BALF was obtained by three slow injections of 10 mM PBS (0.5 ml) into the trachea using a cannula (total volume of 1.5 ml). The BALF supernatants and serum samples were stored at -80°C until biochemical analysis was performed.

2.5. Cytological and biochemical analysis

The total leukocytes and differential cell numbers in the BALF were measured using a Technicon H1E Hematology System (Bayer Corporation, Tarrytown, NY, USA). IgE concentrations in the serum and IL-4 and IL-5 concentrations in the BALF were determined by enzyme-linked immunosorbent assays using kits for mouse IgE, IL-4 and IL-5 (IgE Quantitation Kit, BETHYL Laboratories, Inc., IL-4 BD OptEIA, Pharmingen; and IL-5 BD OptEIA, Pharmingen).

2.6. Histological examination

The lungs were infused via the trachea with 1 ml of 10% neutral formalin and immersed in the same fixative for at least 24 h. Tissues were embedded in paraffin, and sections (4 μm) were cut and stained with hematoxylin and eosin, according to standard protocols.

2.7. Statistical analysis

All data are presented as means $\pm$ standard deviations (SD). The statistical significance of the differences between the groups was analyzed by the Tukey–Kramer Honestly Significant Difference (HSD) test following ANOVA for multiple comparisons using JMP ver 5.1 (SAS Institute, Cary, NC, USA). A p value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Body weight change

The body weight gains in mice sensitized with OVA were similar to those of non-asthmatic mice (Table 1). Although dexamethasone treatment significantly reduced the growth of asthmatic mice, dietary administration of MSG did not affect growth compared to mice fed the basal diet.

3.2. Pulmonary infiltration of eosinophils

The number of eosinophils in the BALF was used to characterize pulmonary inflammation after the OVA challenge. The effects of MSG intake on pulmonary inflammation were assessed by measuring the infiltration of eosinophils into the BALF (Fig. 1). No eosinophils were detected in the BALF collected from non-asthmatic control animals. The obvious appearance of eosinophils in the BALF indicated pulmonary infiltration of these cells in OVA-sensitized asthmatic mice. Four weeks of feeding with the 0.5% or 5% MSG-supplemented diet did not affect the number of eosinophils in the BALF of OVA-sensitized mice (Fig. 1A). Oral gavage administration of MSG solution (0.5% or 5%) 30 min before the assessment did not affect the presence of these cells in the BALF (Fig. 1B), indicating that MSG ingestion had no acute effects on the pulmonary infiltration of eosinophils in asthma model mice. In contrast, dexamethasone treatment (1 mg/kg, i.p., 3 times/week) during

Table 1

The effects of MSG on growth and food intake.

Dietary MSG (%, w/w)	Dexamethasone treatment	Body weight gain (g/week)	Food intake ¹ (g/d)
<i>Non-asthmatic control mice</i>			
0%	None	1.4 ± 0.5^a	3.20
<i>OVA-sensitized asthmatic mice</i>			
0%	None	1.1 ± 0.4^a	2.94
0.5%	None	1.2 ± 0.3^a	2.90
5%	None	1.3 ± 0.4^a	2.83
0%	1 mg/kg ²	0.5 ± 0.6^b	2.61

Body weight gain and food intake of asthmatic and non-asthmatic mice fed an experimental diet containing 0%, 0.5% or 5% MSG were recorded during the 3-week OVA sensitization period. The data are expressed as means $\pm$ SD ($N = 8/\text{group}$). Values without a common letter differ significantly, $p < 0.05$ (Tukey's HSD test).

¹ The mean values of the 12 animals in each group.

² The mice were injected intraperitoneally with 1 mg/kg of dexamethasone 3 times per week.

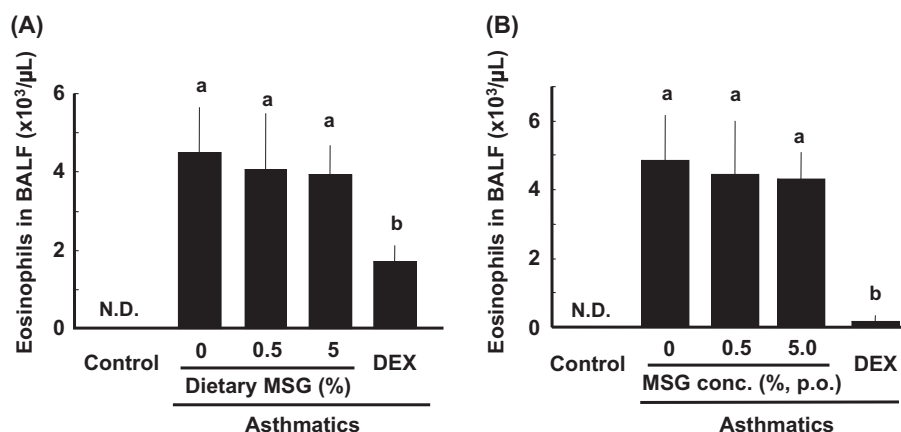


Fig. 1. Eosinophilic cell count in the BALF. The number of eosinophilic cells in the BALF obtained from each mouse was calculated. Control: non-asthmatic mice. DEX: asthmatic mice treated with dexamethasone (1 mg/kg, i.p.) three times per week for 3 weeks of OVA sensitization. (A) MSG was administered in the feed (0%, 0.5% or 5% w/w) during the 3-week OVA sensitization period and during the preceding week. (B) MSG was administered via oral gavage (0%, 0.5% or 5% solution, w/w) 30 min before the assessment. The data are expressed as means $\pm$ SD ($N = 8$ –12/group). Values without a common letter differ significantly, $p < 0.05$ (Tukey's HSD test). N.D.: not detected.

the OVA sensitization period significantly reduced the migration of eosinophils into the BALF.

3.3. Concentrations of Th2-type cytokines in the BALF

The production of cytokines such as IL-4 and IL-5 is a feature of a robust Th2 response and is characteristic of pulmonary reactions in asthma. The concentrations of these Th2-type cytokines were measured in the BALF as indicators of the pulmonary production of these cytokines (Fig. 2). The concentrations of IL-4 and IL-5 in the BALF were significantly higher in OVA-sensitized asthmatic mice compared to non-asthmatic control mice ($p < 0.01$). These increases in OVA-sensitized mice were partially prevented by dexamethasone treatment. Besides, 4-week feeding of an experimental diet containing either 0.5% or 5% MSG to asthma model mice did not affect the concentration of IL-4 or IL-5 in the BALF relative to feeding an MSG-free diet. These observations suggest that ingestion of MSG does not affect the pulmonary production of Th2-type cytokines.

3.4. Concentrations of IgE in systemic circulation

Systemic changes in the model mice were examined by measuring serum concentrations of IgE (Fig. 3). The IgE concentrations

were elevated in asthmatic mice, whereas IgE was undetectable in non-asthmatic control mice. Feeding an MSG-containing diet (0.5% or 5%, w/w) for 4 weeks did not change the serum IgE concentrations in asthma model mice relative to feeding an MSG-free diet, whereas dexamethasone treatment significantly reduced the serum IgE levels.

3.5. Histological changes in the lungs

Lung histology was examined to investigate the extent and anatomical localization of pulmonary inflammation (Fig. 4). The OVA challenge induced goblet cell hyperplasia, mucus hypersecretion and widespread peribronchiolar and perivascular infiltration of inflammatory cells, which were primarily eosinophilic in nature. Four weeks of feeding a diet containing 0.5% or 5% MSG did not affect the changes caused by OVA sensitization. In contrast, dexamethasone treatment (1 mg/kg, i.p.) three times per week for 3 weeks markedly attenuated leukocyte infiltration, the development of goblet cell hyperplasia, and mucus hypersecretion.

3.6. Airway responsiveness to methacholine

A major clinical symptom of asthma is airway hyperresponsiveness leading to respiratory problems due to increased airway resis-

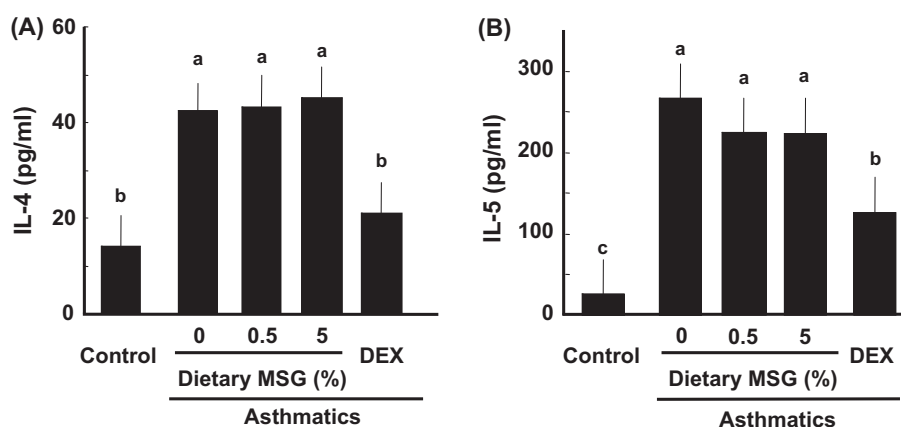


Fig. 2. IL-4 and IL-5 concentrations in the BALF. Concentrations of IL-4 (A) and IL-5 (B) in the BALF were measured by ELISA. Control: non-asthmatic mice. DEX: asthmatic mice treated with dexamethasone (1 mg/kg, i.p.) three times per week during the 3-week OVA sensitization period. MSG: asthmatic mice fed a diet containing 0%, 0.5% or 5% (w/w) MSG for 4 weeks, including the 3-week OVA sensitization period. The data are expressed as means $\pm$ SD ($N = 8$ /group). Values without a common letter differ significantly, $p < 0.05$ (Tukey's HSD test).

tance. The effects of MSG ingestion on the development of airway hyperresponsiveness to methacholine inhalation were investigated by measuring Penh, an indicator of airway resistance. Penh values were elevated following methacholine inhalation in a dose dependent manner in asthmatic and non-asthmatic mice. The OVA challenge significantly increased the Penh values in the asthma model mice compared to the values observed in non-asthmatic control mice at methacholine dosages of 7.25 and 12.5 mg/mL. Four weeks

of feeding MSG-containing diets (0.5% or 5%, w/w) did not affect the Penh values of asthma model mice, indicating that MSG does not affect airway responsiveness to methacholine (Fig. 5A). Oral administration of an MSG solution (15 mL/kg) to asthma model mice at concentrations of 0.5% or 5% (w/w) 30 min before methacholine inhalation did not affect airway resistance at any of the evaluated dosages of methacholine (Fig. 5B). In contrast, dexamethasone treatment (1 mg/kg, i.p.) of the asthma model mice significantly prevented the development of airway hyperresponsiveness to methacholine in both experiments ($p < 0.05$ versus control).

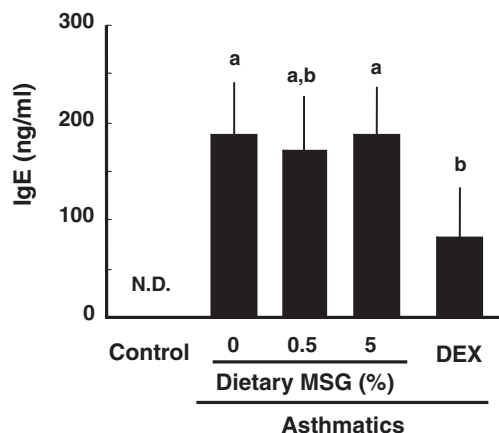


Fig. 3. IgE serum concentrations. Concentrations of IgE in the serum were measured by ELISA. Control: non-asthmatic mice. DEX: asthmatic mice treated with dexamethasone (1 mg/kg, i.p.) three times per week during the 3-week OVA sensitization period. MSG: asthmatic mice fed a diet containing 0%, 0.5% or 5% (w/w) MSG for 4 weeks, including the 3 week OVA sensitization period. N.D.: not detected. The data are expressed as means $\pm$ SD ($N = 8$ /group). Values without a common letter differ significantly, $p < 0.05$ (Tukey's HSD test).

4. Discussion

In the present study, the potential effects of MSG ingestion on disease development in asthma model mice sensitized with OVA were investigated. Eosinophil infiltration in the lungs is a primary inflammatory response in asthma, which precedes hyperplasia and hypertrophy of the bronchial epithelium. The OVA challenge in the present study evoked eosinophil infiltration into the BALF, which was ameliorated by dexamethasone treatment during OVA sensitization. Feeding an MSG-containing diet during the OVA sensitization period and during the preceding week did not affect eosinophil infiltration into the BALF, even with a high concentration (5%) of MSG. These observations indicate that MSG ingestion is not involved in the progression of pulmonary inflammation caused by an OVA challenge. This finding was further supported by histological examination. Dietary MSG ingestion did not decrease the peribronchial or perivascular infiltration of inflammatory cells (including eosinophilic cells) or the secondary response observed in bronchial epithelium. By contrast, these changes were ameliorated by dexamethasone treatment.

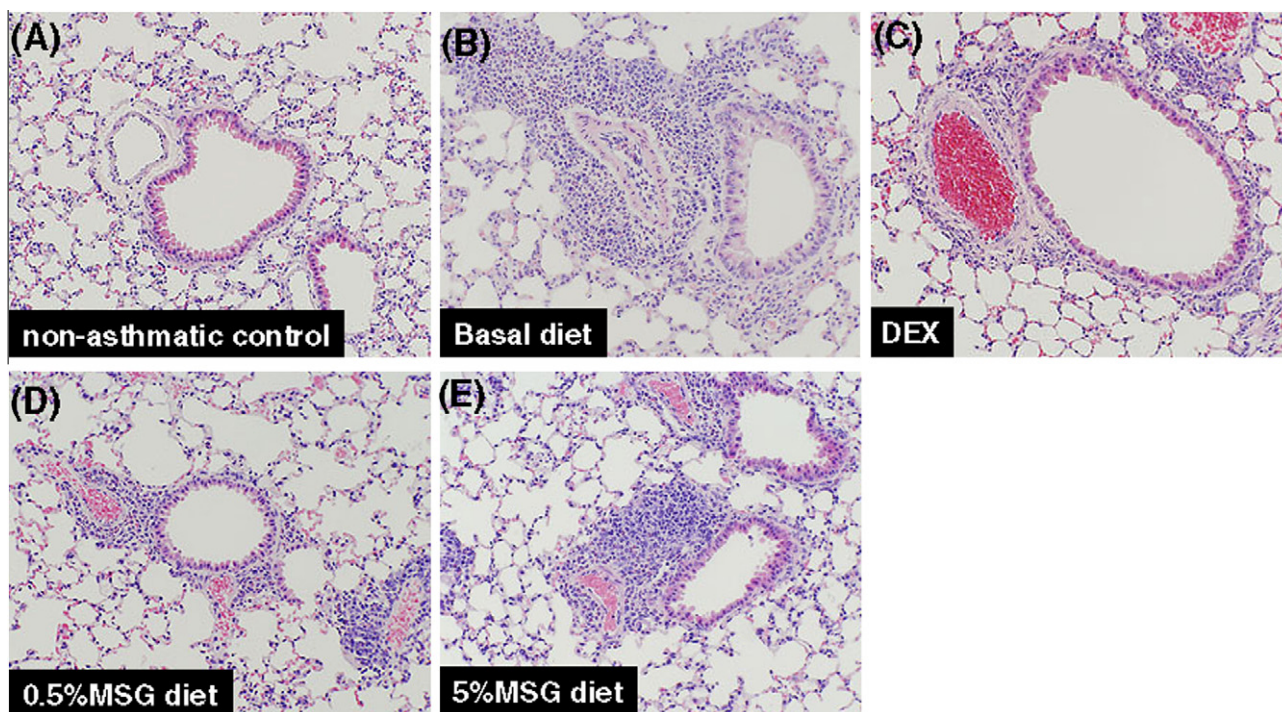


Fig. 4. Histological changes in the lungs. A representative section from each group of eight mice is shown. (A) Non-asthmatic control. (B) OVA-treated asthmatic mice fed a basal diet during the experimental period. Peribronchial and perivascular inflammatory infiltrates, including eosinophilic cells, are seen with mucosal hyperplasia. (C) asthmatic mice treated with dexamethasone (1 mg/kg, i.p.) three times per week during the 3-week OVA sensitization period. Peribronchial and perivascular infiltration of immunocytes and mucosal hyperplasia were ameliorated compared to the control. (D) and (E) asthmatic mice fed a diet containing 0.5% or 5% MSG during the 3-week OVA sensitization period and during the preceding week. No differences were observed in the MSG-fed asthmatic mice compared to the asthmatic mice fed a basal diet (B). H&E staining; magnification, $\times 400$.

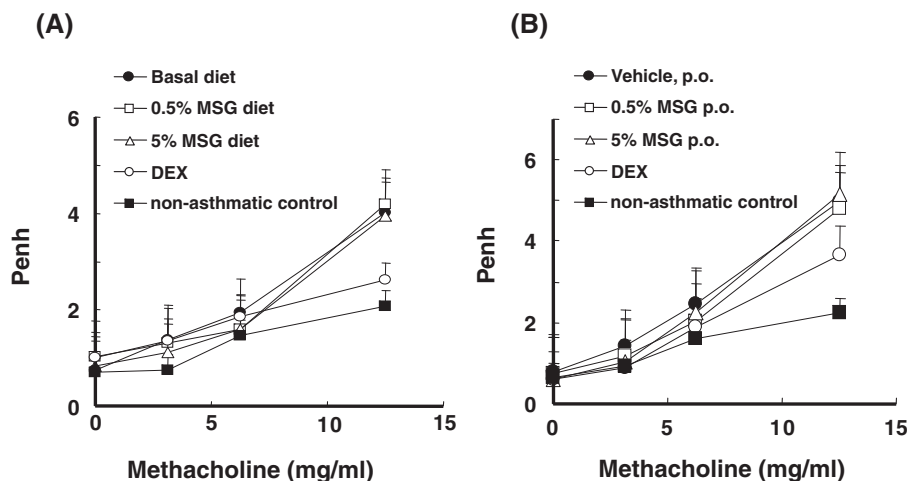


Fig. 5. Airway responsiveness to methacholine. Mouse airway responsiveness to increasing concentrations of methacholine was measured using a single-chamber whole-body plethysmograph (Buxco, Sharon, CT). The mice were challenged with aerosolized methacholine (3.125 mg/ml in solution) for 1 min, and bronchoconstriction was recorded for an additional 5 min, and similarly response for each increasing dose of methacholine (6.25 and 12.5 mg/ml in solution) was assessed. DEX: asthmatic mice treated with dexamethasone (1 mg/kg, i.p.) three times per week during the 3-week OVA sensitization period. (A) MSG was administered in the feed (0%, 0.5% or 5% w/w) during the 3-week OVA sensitization period and during the preceding week. (B) MSG was administered by oral gavage (0%, 0.5% or 5% solution, w/w) 30 min before the assessment. The data are expressed as means $\pm$ SD ($N = 8$ /group).

An increased blood IgE level is another feature of asthma. It is closely associated with allergic inflammation in mouse models of asthma (Hessel et al., 1998). Indeed, a substantial rise in systemic IgE was observed in our mouse model of asthma in the present study. While suppression of inflammation by dexamethasone treatment alleviated the elevation of IgE, dietary addition of MSG did not change the circulating IgE concentrations in the asthmatic mice. These noted changes in blood IgE levels are consistent with the observed inflammatory responses.

Allergic immune diseases, including asthma, are thought to be caused by a Th1/Th2 imbalance, with increases in the Th2 cell population and Th2 cytokines. Th2 cells, i.e. CD4 positive T cells, have been identified in the BALF and in airway biopsies of asthmatics. Th2 cytokines such as IL-4, IL-5, and IL-13 are secreted in the airways of asthmatic patients, even in those with mild or asymptomatic disease (Barnes, 2001). Therefore, pulmonary levels of these Th2 cytokines are considered sensitive indicators of asthmatic progression. Indeed, the OVA challenge in the present study increased the concentrations of both IL-4 and IL-5 in the BALF, and they were lowered following dexamethasone treatment. Dietary administration of 0.5% or 5% MSG during OVA sensitization did not affect IL-4 and IL-5 levels in the BALF, indicating that MSG ingestion did not affect the production of these cytokines or the Th1/Th2 balance in these mice. Th2 cells, through secretion of IL-4 and IL-13, are potent activators of B cell antibody production, particularly IgE (Ryzhov et al., 2004), while IL-5 is critical for eosinophil differentiation and maturation (Ray and Cohn, 1999). Thus, the results described above that dietary administration of MSG did not affect pulmonary infiltration of eosinophils or blood IgE levels in OVA-challenged mice is consistent with the results that MSG ingestion did not amplify Th2 responses in these animals.

Increased airway resistance due to bronchostenosis during an asthma attack is triggered by various stimuli, such as exposure to cold air, contact with irritating substances, mental stress and contact with allergens (Vandenplas and Malo, 2003). The hyperresponsiveness of the airway to such stimuli is of clinical significance in asthma. Therefore, we examined the response to methacholine, a nicotinic substance known to cause airway irritation. Enhanced airway resistance in the OVA-sensitized mice after methacholine inhalation indicated airway hyperresponsiveness to methacholine in these mice. Dietary administration of MSG during OVA sensitiza-

tion did not change the level of airway resistance, regardless of the presence or absence of the methacholine stimulus, indicating that MSG ingestion does not adversely affect respiratory function or the development of airway hyperresponsiveness in asthmatic mice.

The OVA-sensitized asthmatic mouse model utilized here has many similarities to human asthmatics in terms of the characteristic features of type 1 hypersensitivity, such as elevation of IgE and activation of Th2 responses. The responses to steroid therapeutics, including dexamethasone, in this model are also similar to those in humans (Snider et al., 1963). Many reports have suggested adverse effects of tobacco smoke (Barrett et al., 2002; Moerloose et al., 2005) and diesel exhaust particles (DEP) (Senechal et al., 2003) in asthmatic patients. The adverse effects of tobacco smoke and DEP were investigated in this mouse model; both inhalation of tobacco smoke and intratracheal instillation of DEP reportedly enhance OVA-induced allergic inflammatory responses (Barrett et al., 2002; Bleck et al., 2006; Hashimoto et al., 2001). The results described above, which indicated no involvement of continual MSG ingestion in disease development in the asthma model mice, agree with previous clinical studies (Stevenson, 2000). Further, we assessed whether MSG ingestion exerted acute effects on this mouse model. No adverse effects on pulmonary inflammation or airway resistance were observed at 30 min after an oral challenge with either 0.5% or 5% MSG solution. These results agree with those of well-controlled clinical studies by Woods et al. (1998) and Stevenson (2000), in which they did not observe any adverse effects of a single ingestion of MSG on the clinical symptoms of asthmatics.

The relationship between MSG intake and asthma indicated by early clinical works has not been supported by successive well-controlled clinical studies. Recent reviews by Walker and Lupien (2000) and Williams and Woessner (2009) concluded that there is no scientific evidence indicating adverse effects for asthmatic patients from general ingestion of MSG. The present study provides a scientific basis for this conclusion, as use of an animal model enabled us to investigate the effects of MSG in detail through histological and cytological analyses. The dosages of MSG tested here (5% both in the diet and in solution) are considered much higher than the general intake of MSG in humans. A diet containing 5% MSG corresponds to a daily intake of 5 g/kg, a level that is over 100 fold higher than the average daily human exposure to MSG. The concentration of MSG both in the diet and the solution tested

in the present study is also much higher than the general concentration of MSG in food (Halpern, 2000).

In conclusion, the current study demonstrated no adverse effects of continual ingestion of MSG on the development of asthma using an OVA-sensitized asthma mouse model. The results of this study did not reveal acute effects of MSG ingestion on asthmatic symptoms in the mouse model. In addition to a functional assessment, the current study included histological and cytological examinations to confirm the safety of MSG ingestion for asthmatics. These results provide a scientific basis for the observed safety of general MSG intake in asthmatic patients.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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