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Aggravation of Allergic Rhinitis by Air Pollution: Demonstration by an Animal Model of Pollenosis

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1. Introduction

Numbers of patients suffering from allergic diseases, such as asthma, pollenosis, atopic dermatitis, etc. have been increased in industrially advanced countries. The increases are remarkable especially in urban area in such countries.

It has been generally accepted that not only genetic but also environmental factors contribute to the pathogenesis of various diseases. Allergic diseases are also caused by both factors. Genetic factors can be explained by a concept of single nucleotide polymorphism (SNP), which means that only one nucleotide mutation can make a person highly sensitive to allergic diseases. However, the recent increase in the number of allergic patients cannot be explained merely by SNP.

It has been widely indicated that environmental factors such as air pollution, improvement of hygiene, changes in foods and dwelling, etc. are closely associated with the increase in patients.

In this chapter, the relationship between air pollutants and allergic diseases in the airway tissues is Focused on. In order to demonstrate this relationship, experimental animal models of allergic asthma have been widely utilized. First, the findings obtained from animal models are summarized. Second, we have actually evaluated whether the pyrenes present in diesel exhaust particles, cigarette smoke, etc. aggravate allergic rhinitis symptoms in a pollenosis guinea pig model (Mizutani et al., 2007). The methodology of development of this model of pollenosis and the effects of pyrenes on the model are also described.

2. Air pollutants that have been demonstrated to aggravate airway allergic diseases in experimental animal models

Allergic diseases are manifested by antigen-specific IgE antibody formation, increase in Th2 cytokine (IL-4, IL-5, IL-13, etc.) production and decrease in Th1 cytokine (interferon-γ) production. In allergic airway diseases, asthma is a potentially life-threatening disorder, and thus the mechanisms underlying allergen-induced asthmatic responses have been analyzed using murine models not only by measuring levels of IgE antibody and Th2 cytokines, but also by estimating leukocyte infiltration into the lung and especially the eosinophilia, airway hyperresponsiveness to a non-specific stimulus, and airway remodeling.

Various indoor and outdoor air pollutants have been evaluated to determine whether allergic airway diseases are aggravated by exposure to pollutants. Experimental animal models of asthma especially in mice have been extensively utilized to analyze the relationships between air pollutants and disease.

2.1 Diesel exhaust particles (DEPs)

Diesel fuel combustion results in the production of DEPs. DEPs consist of an elemental carbon core with a large surface area, to which hundreds of chemicals such as pyrenes, phenanthrenes, etc. and transition metals such as zinc, aluminium, iron, etc. are attached (Peden & Reed, 2010). In human studies, it was demonstrated that intranasal instillation of DEPs increased nasal IgE antibody secretion. Furthermore, the DEP treatment increased Th2-type cytokine production in the nasal cells. Those findings strongly suggest that exposure to DEPs further aggravates patients' allergic state (Diaz-Sanchez, 1999; Riedl & Diaz-Sanchez, 2005).

In experimental animal models of allergic asthma, it has been reported that exposure to DEPs in mice resulted in enhanced allergen-induced IgE production in serum, airway Th2-type cytokine production, airway hyperresponsiveness, airway eosinophilia, etc. (Munakata, 1986; Takafuji, 1987; Fujimaki, 1994; Suzuki, 1996; Takano, 1997, 1998; Ichinose, 1998; Miyabara, 1998; Steerenberg, 1999; Kobayashi, 2000; Hashimoto, 2001; Liu, 2008). Interestingly, Takahashi et al. (2010) recently demonstrated that long-term mite antigen exposure-induced airway remodelling was also augmented by DEP exposure.

The mechanisms underlying DEP-induced aggravation of allergic responses are currently under investigation. Most studies have reported that exposure to DEPs induces production of reactive oxygen species (ROS) such as superoxide anion, hydrogen peroxide, hydroxy radical, etc., leading to cellular damage. The production of ROS may play important roles in the augmentation of antigen-induced asthmatic responses in the lung (Riedl & Diaz-Sanchez, 2005). Further analyses are required in order to understand the detailed molecular mechanisms of the effects of DEPs.

2.2 Residual oil fly ash (ROFA)

ROFA is an air pollutant produced by the combustion of fossil fuels, and contributes to total primary particulate matter emissions in the United States. ROFA is rich in water-soluble transition metals. Epidemiological and human experimental studies have attributed increased respiratory inflammation to high metal content of pollutants.

It has been demonstrated that exposure to ROFA enhances allergen-induced asthmatic responses in mice (Hamada, 1999; Goldsmith, 1999; Gavett, 1999; Arantes-Costa, 2008). Interestingly, Lambert et al. (2000) reported that water-soluble metals, either $NiSO_4$, VSO_4 or $FeSO_4$ are also capable of enhancing those asthmatic responses, indicating that the enhanced allergic responses by ROFA were mediated by soluble metal constituents. The relationships between environmental metal constituents and asthmatic responses should be further analyzed clinically and experimentally.

2.3 Cigarette smoke

Cigarette smoking has been implicated in the development of diseases in multiple organs, including cardiovascular diseases, malignancy, and respiratory disorders. Among the respiratory diseases, cigarette smoking is one of main causes of chronic obstructive pulmonary disease (COPD).

Epidemiologic studies in asthmatics have reported an association between environmental cigarette smoke (ETS) exposure and asthma symptoms. In asthmatic children, parental smoking increases levels of asthma symptoms and the frequency of asthma exacerbations (Evans, 1987; Chilmonczyk, 1993; Britton, 2005). In experimental animal models, chronic coexposure to ETS increased levels of allergen-induced airway remodelling and airway responsiveness by up-regulating the expression of chemokines (Min, 2007), suggesting that ETS is a risk factor for asthma. Other studies using animal models have also reported that exposure to ETS aggravates airway allergy (Seymour, 1997, 2003, 2005; Rumold, 2001), although there are also controversial reports (Kang, 1996; Boweles, 2005).

In contrast, the effect of mainstream or active cigarette smoking (MTS) on asthma is controversial. MTS has been associated with increased an serum level of IgE and airway hyprresponsiveness (Barbee, 1987; Mitsunobu, 2004). However, other studies in asthmatic patients have failed to find any relationship between MTS and asthma (Siroux, 2000; Vidal, 2004). Even in experimental animal models, the impact of MTS on OVA-induced asthmatic responses in mice is controversial (Robbins, 2005; Moerloose, 2005, 2006; Thatcher, 2008). Thus, the difference between the effects of ETS and MTS on asthma should be further analyzed in experimental studies.

2.4 Nanoparticles

The development of nano-technology has increased opportunities to be exposed to engineered nanomaterials present in the environment. Nanomaterials are included in industrially manufactured products such as ink, toner, cosmetics, latex, etc. However, it has been largely unclear how exposure to these nanomaterials affects human health, especially the airway tissues.

Inoue et al. (2005, 2009a, 2009b) and others (Alessandrini, 2006; de Haar, 2008) have extensively studied the effects of nanoparticles on allergen-induced asthmatic responses in mice, reporting that relatively small diameters of particles induced enhancement of allergic airway inflammation. For example, nanoparticles with a diameter of 14 nm produced more prominent allergic airway inflammation, characterized by infiltration of eosinophils and neutrophils, by an increase in epithelial goblet cell number, and by increases in levels of cytokines and chemokines in the lung than those with a diameter of 56 nm.

Further studies are required to fully understand the mechanisms underlying the aggravation of nanomaterials on the allergic airway inflammation.

2.5 Asian sand dust

Asian sand dust is a dust storm originating in the deserts of China and Mongolia, and heading toward Japan, Taiwan, Korea, etc. It has been recognized that Asian sand dust may be artificially formed by environmental deterioration such as deforestation, etc. The diameters of particles in sand dust are several to several tens of micrometers. Such coarse particles may have limited adverse effects on the respiratory organ. However, recent studies have indicated that Asian sand dust contains sulfates and nitrates (Ro, 2005) that may originate from industrial areas in China. In addition, it was reported that fungi are adsorbed to Asian sand dust (Ichinose, 2008a).

Ichinose et al. (2008b) first reported that exposure to Asian sand dust to OVA-sensitized mice enhanced allergen challenge-induced asthmatic responses including lung eosinophilia, Th2 cytokine and chemokine production in the lungs. More interestingly, they

Air pollutant	Author, publication year	Species	Allergen	Characteristic effects of pollutants on allergic responses
DEP	Muranaka et al., 1986	Mouse	OVA, JPCA	Enhancement of IgE production
	Takafuji et al., 1987	Mouse	OVA	Enhancement of IgE production
	Fujimaki et al., 1995	Mouse	OVA, JPCA	Enhancement of IL-4 production
	Suzuki et al., 1996	Mouse	Mite	Enhancement of IgE and IgG1 production
	Takano et al., 1997	Mouse	OVA	Enhancement of lung eosinophilia and Th2 cytokine production
	Takano et al., 1998	Mouse	OVA	Enhancement of AHR
	Ichinose et al., 1998	Mouse	OVA	Enhancement of lung eosinophilia, airway epithelial damage
	Miyabara et al., 1998	Mouse	OVA	Enhancement of lung eosinophilia, production of Th2 cytokines, and increase in goblet cells in the epithelium
	Steerenberg et al., 1999	Rat	Grass pollen	Enhancement of IgE and IgG1 production
	Kobayashi, 2000	Guinea pigs	OVA	Enhancement of sneezing and nasal eosinophilia
	Hashimoto et al., 2001	Guinea pigs	OVA	Enhancement of IAR and LAR, mucus hypersecretion, lung eosinophilia, and airway vascular permeability
	Liu et al., 2008	Mouse	Af	Hypermethylation of IFN gamma promotor, and hypomethylation of IL-4 promotor
	Takahashi et al., 2010	Mouse	Mite	Enhancement of airway remodelling, AHR, Th2-type airway inflammation
ROFA	Hamada et al., 1999	Mouse	OVA	Enhancement of AHR and airway inflammation
	Goldsmith et al., 1999	Mouse	OVA	Enhancement of AHR
	Gavett et al., 1999	Mouse	OVA	Enhancement of IL-4 and IL-5 production
	Lambert et al., 2000	Rat	HDM	Enhancement of IgE production, bronchoconstriction, lymphocyte proliferation, and Th2 cytokine production
	Arantes-Costa et al., 2008	Mouse	OVA	Enhancement of AHR, and airway epithelial damage
ETS	Kang et al., 1996	Guinea pig	CRa	No change in anaphylactic antibody production Reduction of antigen-induced bronchospasm
	Seymour et al., 1997	Mouse	OVA	Enhancement of IgE and IgG1 production, lung eosinophilia, Th2 cytokine production
	Rumold et	Mouse	OVA	Enhancement of IgE and IgG1 production, lung

	al., 2001			eosinophilia, Th2 cytokine production
	Seymour et al., 2003	Mouse	Af	Enhancement of AHR, eosinophilia, and Th2 cytokine production
	Boweles et al., 2005	Mouse	OVA	Neither change in AHR, IgE production nor airway inflammation
	Seymour et al., 2005	Mouse	Af	Enhancement of nitric oxide production
	Min et al., 2007	Mouse	OVA	Enhancement of AHR, airway remodelling, epithelial chemokine expression, and increase in TGF-b$^+$ cells
MTS	Robbins et al., 2005	Mouse	OVA, RW	Enhancement of cytokine production Reduction of lung eosinophilia, Th2 cytokine production and AHR Neither change in IgE nor IgG1 production
	Moerloose et al., 2005	Mouse	OVA	Enhancement of airway inflammation and responsiveness
	Moerloose et al., 2006	Mouse	OVA	Enhancement of IgE production, increases in eosinophils, CD4$^+$ T cells, and goblet cell in the lung No change in AHR
	Thatcher et al., 2008	Mouse	OVA	Reduction of airway eosinophilia, goblet cell metaplasia, IL-4 and IL-5 production, and IgE production
Nano Ps	Inoue et al., 2005	Mouse	OVA	Enhancement of IgE production and airway inflammation
	Alessandrini et al., 2006	Mouse	OVA	Enhancement of BAL cellularity, Th2 cytokine production, AHR, mucus production
	de Haar et al., 2008	Mouse	OVA	Enhancement of proliferation of CD4$^+$ cells, cytokine production, expression of co-stimulatory molecules
	Inoue et al., 2009a	Mouse	OVA	Enhancement of IgE production and airway inflammation (by carbon nanotubes)
	Inoue et al., 2009b	Mouse	OVA	Enhancement of IgE production and airway inflammation (by latex nanomaterials)
ASD	Ichinose et al., 2008b	Mouse	OVA	Enhancement of IgE production, lung eosinophilia, goblet cell proliferation, cytokine production
	Ichinose et al., 2009	Guinea pig	JCPA	Enhancement of nasal obstruction, histamine and CysLT release in NCLF, nasal eosinophilia, and IgE production Neither change in sneezing nor nasal secretion

Table 1. Representative studies evaluating relationship between air pollutants and airway allergic responses using experimental animal models. Abbreviations: Af, Aspergillus fumigatus; AHR, airway hyperresponsiveness; ASD; Asian sand dust, BAL; bronchoalveolar lavage fluid, CRa; cockroach allergen, CysLT; cysteinyl leukotriene, DEP; diesel exhaust particles, ETS; environmental tobacco smoke, IAR; Immediate asthmatic response, IL; interleukin, JCPA; allergen of Japanese cedar pollen, LAR; late asthmatic response, MTS; mainstream cigarette smoke, Nano Ps; nano particles, NCLF; nasal cavity lavage fluid, OVA; ovalbumin, ROFA; residual oil fly ash, RW; ragweed

demonstrated that allergic rhinitis symptoms induced by Japanese cedar pollen in guinea pigs were also augmented by exposure to Asian sand dust (Ichinose, 2009).
However, the relationship between Asian sand dust and health problems remains inconclusive, and further epidemiological and experimental studies are required.

3. Aggravation of allergic rhinitis by pyrenes: Demonstration by Japanese cedar pollen-induced allergic rhinitis model of guinea pigs

Pyrenes, such as benzo(a)pyrene (BaP) and 1-nitropyrene (1-NP), which are encountered in the environment mainly in the form of air pollution, are ubiquitous environmental pollutants found in DEP and cigarette smoke (Rosenkranz, 1980; Scheepers, 1995; Bai, 1998; Ohura, 2004). Carcinogenic and mutagenic effects of BaP and 1-NP in various cell types have been well documented (Bai, 1998; el-Bayoumy, 1995; Nakanishi, 2000). In addition, exposure to BaP enhances allergen-induced IgE and Th2 cytokine productions in mice (Kanoh, 1996; Kadkohda, 2005).
As described above, analyses of the relationships between air pollutants and airway allergy have been conducted using asthmatic mouse models. Meanwhile, pollenosis is a major health problem in Japan because the proportion of people with pollenosis in this country has been estimated to be more than 30%. Although the allergic symptoms of pollenosis, such as rhinitis and conjunctivitis, are not life-threatening like the airway obstructive response in asthma, chronic nasal blockage considerably lowers the quality of life of pollenosis patients. In addition, the nasal tissue is the first organ that contacts not only allergens but also air pollutants. Furthermore, "global warming" could increase the quantity of pollen from trees; it was experimentally demonstrated that a doubling of the atmospheric CO_2 concentration significantly stimulated ragweed pollen production (Wayne, 2002), suggesting that the health problem associated with pollens may be further exacerbated in future. Thus, the exposure effects of air pollutants on pollenosis should also be thoroughly examined.
We have established an experimental allergic rhinitis model in sensitized guinea pigs, using Japanese cedar pollen as the antigen (Nabe, 1997a, 1998). This experimental model has been used to assess whether short and long-term daily treatment with pyrenes, BaP and 1-NP aggravate antigen-induced sneezing and nasal blockage (Mizutani, 2007).

3.1 Development of an allergic rhinitis model showing nasal blockage

Japanese cedar pollen is also an air pollutant in the spring in Japan, and the most prevalent pollenosis allergen in this country. Thus, we have used cedar pollen as an allergen for development of an animal model of allergic rhinitis.
To begin with, we attempted to develop an animal model of allergic rhinitis that clearly shows allergic nasal symptoms including sneezing and nasal blockage like the patients. The guinea pig has long been used as a species showing a high responder of bronchial smooth muscle to various endogenous molecules such as histamine, cysteinyl leukotirenes, etc. Thus, we and others have used guinea pigs as a model animal of allergic asthma (Hutson, 1988; Matsumoto, 1994; Nabe, 1997b). From our experience of using of this species in asthma, we also used the guinea pig to develop an experimental model of allergic rhinitis.
In a disease model that can be utilized for pharmacological examinations and analyses of pathogenesis of diseases, several important considerations arise as follows: 1) The model animal should clearly exhibit symptoms that are similar to patients with the disease and actually torment patients, 2) symptoms should be reproducibly caused by reproducible methods, 3) symptoms can be measured as quantitatively as possible.

To satisfy these points, as shown in Fig. 1 (upper panel), guinea pigs were intranasally sensitized with the pollen extract+$Al(OH)_3$, and then intranasally challenged by a quantitative inhalation of the pollen once a week for several months (Nabe, 1997a). After the respective pollen challenge periods, the allergen-specific IgE antibody level in serum was measured, sneezing frequency was counted, and the degree of nasal blockage was assessed by measuring specific airway resistance (sRaw) using a double-flow plethysmograph system.

Because a major antigen protein in Japanese cedar pollen is Cry j 1, the amount of Cry j 1-specific IgE antibody in the serum was measured until the 29th challenge. Consequently, Cry j 1-specific IgE antibody level was increased during the repeated pollen challenges (Fig. 1, lower left panel) (Nabe, 1997a, 2005). In addition, after respective pollen challenges, sneezing was induced within 1 h after a challenge (Nabe, 1998). Regarding nasal blockage, both early and late phase nasal blockage were induced with their respective peaks at 1-2 h and 4-6 h after pollen challenges. The magnitude of biphasic nasal blockage was enhanced until the 7th challenge, followed by induction of almost reproducible nasal blockage after respective pollen challenges until around 30 challenges (Nabe, 1998). Images of the time-course of sneezing, and early and late phase nasal blockage after a certain challenge period are illustrated in the lower right panel of Fig. 1.

Induction of sneezing and biphasic nasal blockage was very similar to the symptoms of allergic rhinitis in pollenosis patients. Although nasal secretion is also a characteristic sign in the patients, and could be clearly observed in the model guinea pigs, we did not attempt to quantify the secretions.

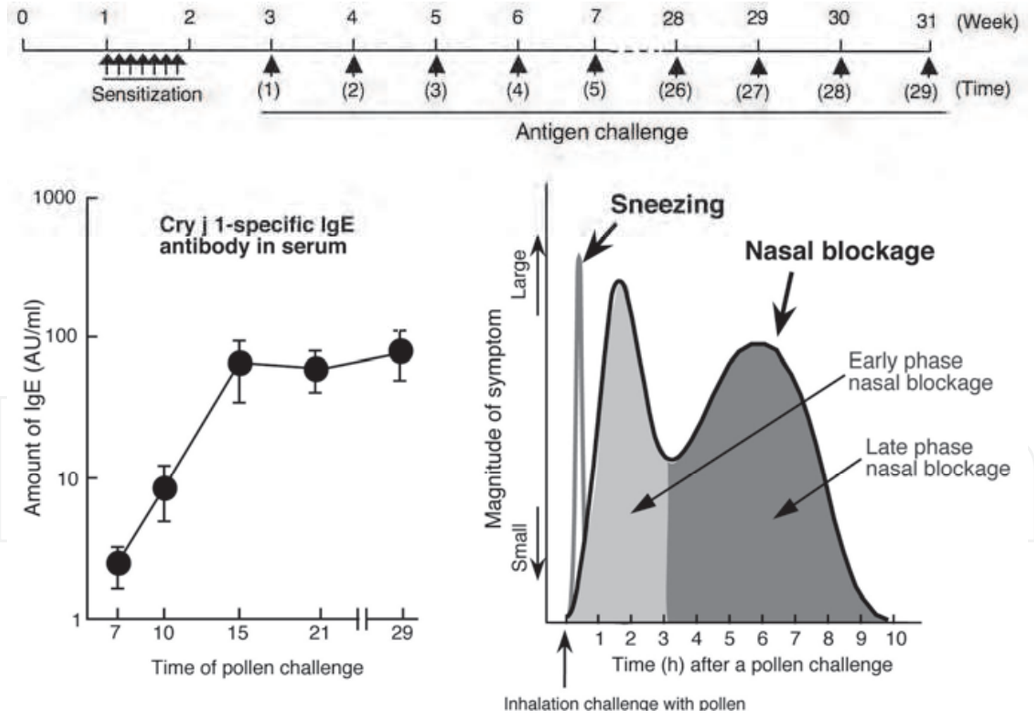

Fig. 1. Schedule for sensitization and challenge with Japanese cedar pollen in guinea pigs (upper panel), time-course change in amount of Cry j 1-specific IgE antibody in the serum during the sensitization and challenge period (lower left panel), and images of time-course changes in sneezing and nasal blockage induced after a certain period of pollen challenge. Each value in the lower left panel represents the mean±S.E. of 8 animals.

3.2 Aggravation of pollen-induced nasal blockage by BaP and 1-NP

As shown in Fig. 2 (upper panel), guinea pigs that had been sensitized with pollen extract plus $Al(OH)_3$ were repeatedly challenged with the pollen once a week. From 6 days before the first sensitization, BaP (100 μg/10 μl per nostril) or 1-NP (10 μg/10 μl per nostril) was daily administered into both nostrils (Fig. 2, upper panel). As expected, BaP aggravated both the early and late phase nasal blockage with statistical significance, and 1-NP also significantly enhanced the late phase response (Fig. 2, lower left and middle panels). In contrast, neither sneezing frequency nor the increase in Cry j 1-specific IgE antibody were affected even by long-term treatment (Fig. 2, lower right panel, and Table 2) (Mizutani, 2007).

Unexpectedly, a relatively short period (2 weeks) of treatment with BaP or 1-NP failed to significantly affect the magnitudes of early and late phase nasal blockage or the sneezing frequency (Mizutani, 2007).

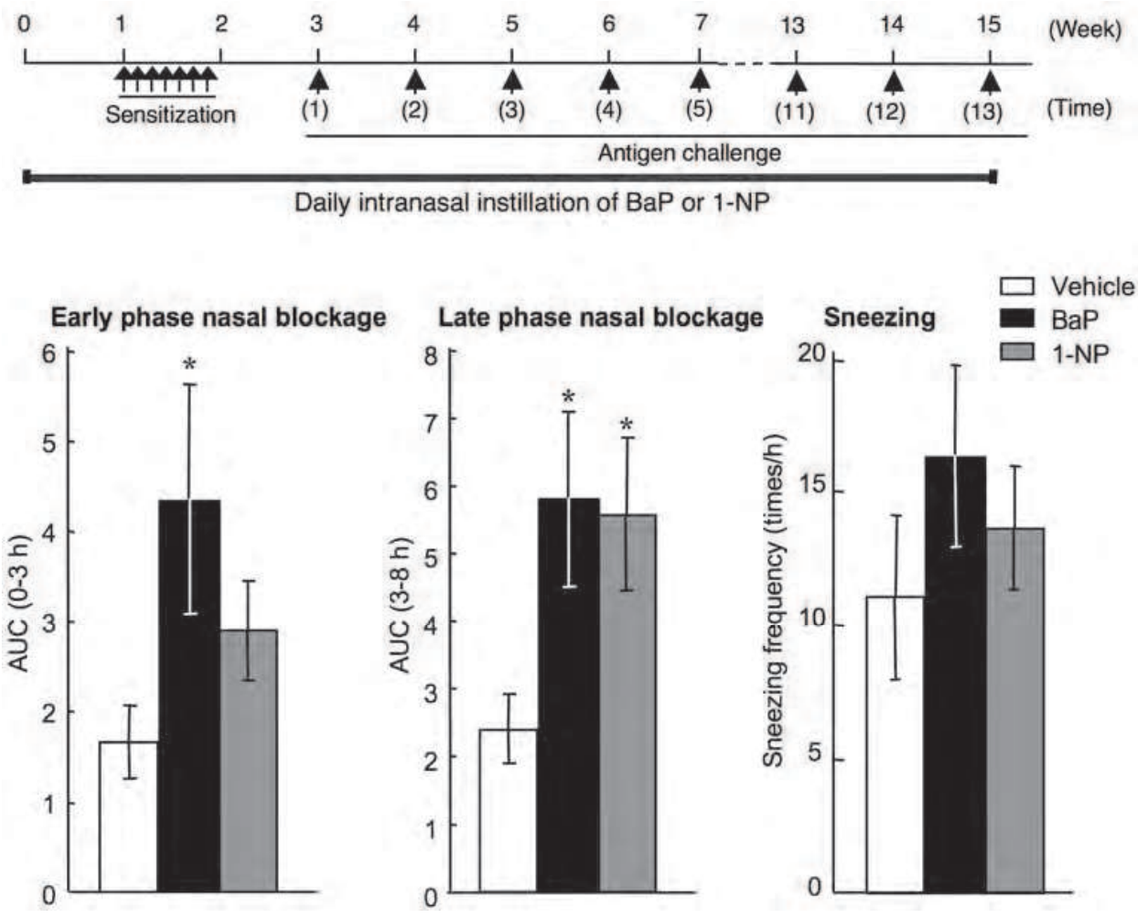

Fig. 2. Schedule for exposure to benzo(a)pyrene (BaP) or 1-nitropyrene (1-NP) during the sensitization and challenge period (upper panel), and effects of BaP and 1-NP on induction of the early and late phase nasal blockage (lower left and middle panels) and sneezing (lower right panel). Each column represents the mean±S.E. of 10 animals. AUC 0-3 h: Area under the curve for increase in sRaw in 0-3 h after the pollen challenge, AUC 3-8 h: Area under the curve for increase in sRaw in 3-8 h after the challange.

We have reported that sneezing is mediated mainly by histamine that is released from the nasal mucosal mast cells via antigen-IgE antibody reaction (Yamasaki, 2001; Fukuda, 2003). Our findings suggest that the pyrenes did not affect the antigen-IgE antibody reaction of mast cells. Meanwhile we have previously suggested that oxidative stress can be closely associated with the induction of biphasic nasal blockage (Mizutani, 2008). As other studies have demonstrated that BaP induces an increase in oxidative stress (Jeng, 2010; Gao,2011), the BaP-induced enhancement of nasal blockage may be due to increased oxidative stress.
The aggravation of nasal blockage was reduced by cessation of the exposure to pyrenes in our model of pollenosis (Mizutani, 2007), indicating that avoidance of air pollutants is an appropriate method for treating the allergy.

	Amount of IgE (AU/ml)
Vehicle	45.3±19.5
BaP	49.1±22.0
1-NP	32.9±11.5

Table 2. Effects of benzo(a)pyrene (BaP) and 1-nitropyrene (1-NP) on the increase in Cry j 1-specific IgE at the 13th pollen challenge in sensitized guinea pigs. Each value represents the mean±S.E. of 10 animals.

4. Conclusion

It has been experimentally demonstrated that air pollutants such as DEP, ROFA, cigarette smoke, nanoparticles, Asian sand dust, etc. can aggravate allergic disorders. Exposure to those environmental pollutants in genetically allergic persons could synergistically aggravate their allergic symptoms. In future, both epidemiological and experimental analyses of the relationships between all candidate pollutants and allergic diseases are further required.

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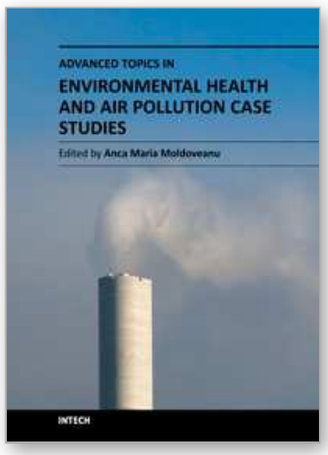

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