ABSTRACT

Purpose: This study aimed to investigate the impact of short-term haze exposure on nasal inflammation in healthy volunteers.

Methods: Thirty-three healthy university students were assessed for nasal symptoms, nasal patency, upper and lower respiratory tract nitric oxide (NO) as well as inflammatory mediators and neuropeptides in nasal secretions before and after a 5-day haze episode. Peripheral blood mononuclear cells (PBMCs) were stimulated with particulate matter with an aerodynamic diameter of less than 2.5 μm (PM$_{2.5}$), and cytokines in the supernatants were examined.

Results: Mild nasal symptoms were reported by some participants during the haze episode. Objective measures of nasal patency demonstrated that nasal airway resistance was significantly increased from baseline levels, while nasal cavity volume and minimum cross-sectional area were significantly decreased. Similarly, the levels of nasal and exhaled NO, eotaxin, interleukin (IL)-5, chemokine (C-C motif) ligand 17, IL-8, substance P, nerve growth factor and vasoactive intestinal peptides in nasal secretions were significantly increased from baseline values following the haze episode. In contrast, the levels of interferon-γ, IL-10, transforming growth factor-β and neuropeptide Y were significantly decreased. Incubation with 0.1 - 10 μg/mL PM$_{2.5}$ significantly increased release of IL-1β, IL-4, IL-5, IL-8 and IL-10 from PBMCs.

Conclusions: Short-term haze exposure may lead to nasal inflammation and hypersensitivity in healthy subjects predominantly by Th2 cytokine-mediated immune responses.

Keywords: Air pollution; particulate matter; nasal inflammation; cytokines; neuropeptides

INTRODUCTION

Air pollution has become a serious problem over the last decade in China, with hazardous dense haze affecting most parts of the Northern and Eastern China. During a haze episode, the concentrations of many airborne pollutants, especially PM$_{2.5}$ (particulate matter with an aerodynamic diameter of less than 2.5 μm), are increased and have the potential to adversely impact public health by affecting the respiratory, cardiovascular and the nervous systems. Furthermore, outdoor pollution can also adversely affect the prevalence of upper airway diseases. An increase in annual PM$_{2.5}$ of 10 μg/m$^3$ was positively associated with the...
prevalence of allergic rhinitis and asthma. However, the relationship between air pollution and nasal inflammation is far from clear.

Nasal epithelium is the first line of defense of the respiratory tract and may be affected acutely by airborne pollutants. Compared to numerous studies documenting the relationship between air pollution and lower respiratory tract diseases, such as asthma, chronic obstructive pulmonary disease, bronchiectasis and cystic fibrosis, few studies have investigated the effects of haze exposure on nasal health, especially in healthy subjects. The aim of the present study was thus to investigate the effect of a short-term haze exposure on nasal symptoms, patency and inflammation in a group of young healthy volunteers living in downtown Beijing.

MATERIALS AND METHODS

Subject selection
Thirty-three healthy adult volunteers (15 females and 18 males) aged 26 to 33 years were recruited from Capital Medical University. According to the questionnaire survey completed at the beginning of the study, all participants lived in a university community in Dongcheng district, Beijing, China. During the study, all participants led a regular life style, including about 3 hours of outdoor activity per day during the university term. All subjects were non-smokers with no history of lung disease and were free of upper or lower respiratory tract infections for at least 4 weeks prior to enrolment in the study. To be eligible for participation in the study, all were additionally required to demonstrate negative skin prick test results to a panel of common allergens, including house dust mite (HDM) (Der f and Der p), seasonal grass pollens (Giants Ragweed, Mugwort, Lamb's quarters, Humulus and Chenopodium album), animal hair, molds and cockroach (Allergopharma, Reinbeck, Germany). The study protocol was conducted in accordance with Declaration of Helsinki, and was approved by the Ethics Committee of Beijing Institute of Otolaryngology. Each participant gave informed written consent before enrolment.

Study protocol
All participants attended our clinic for the baseline assessment visit on March 22, 2014, before which the daily average ambient PM$_{2.5}$ concentration was lower than 100 µg/m$^3$ for 5 consecutive days. Each participant underwent an interview with the investigator and reported any nasal symptoms, including nasal congestion, secretion, dryness, irritation, unpleasant smell and pain in the past 5 days. Each participant was also assessed for nasal patency by rhinomanometry, and exhaled nasal and oral nitric oxide (NO) levels were measured. Nasal secretions were also obtained for the measurement of inflammatory cytokines and neuropeptides at the end of the visit. The participants returned to the clinic after 1 week (March 29, 2014), and again underwent the interview and all laboratory procedures at baseline visit.

Collection of ambient pollutant data
Daily district-specific data on ambient PM$_{2.5}$ as well as PM$_{10}$, SO$_2$, CO, NO$_2$ and O$_3$ were obtained from Beijing Municipal Environmental Monitoring Center for the Dongsu monitoring site in the Dongcheng district of Beijing. The direct distance from the monitor site to the dormitory is approximately 4 km.
Nasal patency
Eccovision acoustic rhinomanometry (Hood Labs, Pembroke, MA, USA) was performed to measure minimum cross-sectional area (MCA) and total nasal cavity volume (NCV) at a distance of 0–5 cm from the opening of the nostril. The ATMO 300 Rhinomanometer (ATMOS Medizin Technik GmbH&Co., Lenzkirch, Germany) was used to measure unilateral nasal airway resistance (NAR) at a 75 Pa point (R\text{75}) by anterior active rhinomanometry, and the total NAR (R\text{75T}) was calculated using the formula (R_t = R_l \times R_r/R_l + R_r). All measurements were taken in a quiet examination room at a temperature of 24°C ± 1°C and a humidity of 70% ± 1%.

Exhaled nasal NO (nNO) and exhaled NO (eNO)
Exhaled nNO was measured using the NIOX® NO analyser (Aerocrine, Solna, Sweden) as described by Krämer et al.13 Briefly, NO-free air was aspirated through the nasal cavity at a flow rate of 50 mL/s, and the participant exhaled slowly against a resistance, which resulted in an introral pressure of approximately 10 cmH\text{2}O, and ensured closure of the velum to prevent mixing of oral and nasal gas. Nasal gas from this circuit was continuously routed in part directly into the NO analyser, and the level of nNO was recorded from a plateau lasting for at least 3 seconds. The procedure was repeated 3 times and a mean nNO (ppb) concentration of 3 readings was used. The eNO was measured at a flow rate of 50 mL/s during a 10-second period with the NO analyser. Again, 3 consecutive eNO values were measured and the mean value was calculated.

Inflammatory cytokines and neuropeptides in nasal secretion
Nasal secretions were collected and processed as described by Watelet et al.14 Briefly, nasal secretions were obtained by inserting a sinus packing bilaterally on the floor of the nasal cavity between the septum and the inferior turbinate for 5 minutes and collected in sterile polypropylene test tubes (Falcon; Becton-Dickinson Labware, Franklin Lakes, NJ, USA). The sinus packs were kept at room temperature for 1 hour (to imitate sampling under clinical conditions) and then stored at 4ºC until assessment of various inflammatory mediators. Two millilitres of 0.9% NaCl solution were added to each sample pack, and the samples were stored at 4ºC for 2 hours prior to recovery of the secretions in the packs by centrifugation at 1,500 g for 15 minutes at 4ºC. The supernatants were collected and stored in aliquots at −20ºC until analysis for the inflammatory mediators.

Nine cytokines, including interleukin (IL)-5, IL-8, IL-10, interferon (IFN)-γ, IL-17A, transforming growth factor (TGF)-β1, TGF-β2, chemokine (C-C motif) ligand 17 (CCL17) and eotaxin in the nasal secretions, were measured using the human magnetic Luminex screening assay (R&D Systems, Minneapolis, MN, USA) and analysed on a Luminex 100 analyser (Luminex 100 System; Luminex Corp., Austin, TX, USA). Similarly, 4 neuropeptides, including substance P (SP), neuropeptide Y (NPY), nerve growth factor (NGF) and vasoactive intestinal peptide (VIP), were assayed using commercial enzyme-linked immunosorbent assay kits (R&D Systems).

Impact of PM\text{2.5} on cytokine secretion from peripheral blood mononuclear cells (PBMCs)
Blood was collected from 8 of the above-mentioned volunteers, and PBMCs were isolated from each sample using Ficoll-Plaque Plus density gradient centrifugation (Amersham Biosciences, Amersham, UK). The cells in each sample were adjusted to a concentration of 2 × 10^6 cells/mL, and 0.5 mL of cell suspension from each sample was incubated with 0.1 μg/mL PM\text{2.5}, 10 μg/mL PM\text{2.5}, or phosphate-buffered saline for 24 hours at room temperature.
At the end of incubation, the samples were centrifuged at 1,500 g for 15 minutes at 4°C, and
the levels of IL-1β, IL-4, IL-5, IL-8, IL-10, IL-13, IL-33, eotaxin, TGF-β1, TGF-β2, TGF-β3 and IFN-γ in the supernatants, were assessed using Luminex bead array technology as mentioned above.

**Statistical analysis**
All statistical analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard error of the mean of the replicate samples, and the paired t-test and the Wilcoxon signed rank test were performed to compare the significance of differences in data from the 2 visits. Values of $P < 0.05$ were considered statistically significant.

**RESULTS**

**Beijing experiences severe air pollution during the study period**
During the study, Beijing was experiencing a haze episode with a daily average ambient PM$_{2.5}$ concentration of 193.0 ± 30.2 µg/m$^3$ for 5 consecutive days, which is about 7.7-times higher than the recommended World Health Organization (WHO) threshold. [15] Fig. 1 shows the daily district-specific data for PM$_{2.5}$ and other pollutants (PM$_{10}$, SO$_2$, CO, NO$_2$ and O$_3$) measured by Beijing Municipal Environmental Monitoring Center (http://zx.bjmemc.com.cn). March 22nd, 2014 was selected as the baseline visit day because the air quality of Beijing was relatively good, with 24-hour mean PM$_{2.5}$ concentration of the previous 5 consecutive days being < 100 µg/m$^3$ (39.6 ± 12.2 µg/m$^3$). Haze pollution in Beijing lasted for 5 consecutive days before the second clinic visit on March 29th, with 24-hour mean PM$_{2.5}$ concentration being >100 µg/m$^3$ (193.0 ± 30.2 µg/m$^3$). The 24-hour mean concentration profiles of PM$_{10}$, SO$_2$, CO, NO$_2$ and O$_3$ followed trends consistent with those of PM$_{2.5}$.

**Haze exposure adversely affects nasal symptoms and nasal patency**
None of the participants reported nasal symptoms at baseline visit; however, during the haze episode, 25 (75.8%) subjects complained of mild nasal symptoms including nasal congestion.

![Fig. 1. Time course of 24-hour mean air pollutant concentration in Beijing between March 17th and 29th of 2014. The left Y axis stands for ambient PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$ and O$_3$ (µg/m$^3$); the right Y axis stands for ambient CO (mg/m$^3$). Visits 1 and 2 took place on March 22nd and March 29th, respectively. Before the baseline visit the 24-hour mean PM$_{2.5}$ concentration was lower than 100 µg/m$^3$ for 5 consecutive days, whereas before the second visit, Beijing had experienced a haze episode for 5 consecutive days with 24-hour mean PM$_{2.5}$ concentration higher than 100 µg/m$^3$.](https://e-aair.org)
The NAR of the participants increased significantly from a baseline value of 0.18 ± 0.01 to 0.23 ± 0.01 Pa/cm³/s (P < 0.001, Fig. 2A), while the NCV decreased significantly from a baseline value of 15.01 ± 0.44 to 7.99 ± 0.61 cm³ (P < 0.001, Fig. 2B). Similarly, the MCA decreased significantly from a baseline value of 1.19 ± 0.04 to 1.09 ± 0.04 cm² (P < 0.05, Fig. 2C). The nasal symptoms experienced by the participants, especially nasal congestion, were consistent with increased NAR, and decreased NCV and MCA during the haze episode.

Haze exposure increases nNO and eNO

Fig. 3 demonstrates the levels of exhaled nNO and eNO levels before and after haze pollution, and shows that both exhaled nNO (198.1 ± 5.6 vs. 245.3 ± 5.9 ppb, P < 0.001; Fig. 3A) and eNO (10.34 ± 0.71 vs. 19.30 ± 1.01 ppb, P < 0.001; Fig. 3B) were significantly increased from baseline levels following the haze episode.

Haze exposure alters nasal inflammatory status as indicated by inflammatory mediators in secretions

Fig. 4 demonstrates that exposure to haze for 5 days resulted in significant increases in eotaxin (70.38 ± 4.24 vs. 108.8 ± 8.15 pg/mL, P < 0.001; Fig. 4A), IL-5 (3.23 ± 0.32 vs. 5.33 ± 0.61 pg/mL, P < 0.001; Fig. 4B), CCL17 (24.03 ± 3.23 vs. 40.31 ± 3.99 pg/mL, P < 0.001; Fig. 4C) and IL-8 (1,222 ± 117.2 vs. 2,160 ± 255 pg/mL, P < 0.001; Fig. 4D) from baseline. In contrast, there was a significant attenuation in the levels of IL-10 (15.27 ± 1.68 vs. 7.90 ± 1.15 pg/mL, P < 0.001; Fig. 4F), TGF-β1 (179.5 ± 17.71 vs. 103.5 ± 12.14 pg/mL, P < 0.001; Fig. 4G) and TGF-β2 (502.4 ± 60.96 vs. 340 ± 40.93 pg/mL, P < 0.001; Fig. 4H) as well as IFN-γ (29.8 ± 2.96 vs. 13.75 ± 1.88 pg/mL, P < 0.001; Fig. 4E), a Th1-type cytokine. The level of the Th17-
type cytokine IL-17 (9.88 ± 0.91 vs. 10.94 ± 0.96 pg/mL, *P* = not significant; Fig. 4I) was not significantly altered.

**Neuropeptides in nasal secretion**

The effect of haze exposure on the levels of neuropeptides in nasal secretions is shown in Fig. 5. SP (323.7 ± 29.63 vs. 556.4 ± 47.06 pg/mL, *P* < 0.001; Fig. 5A), NGF (22.94 ± 3.29 vs. 100.1 ± 14.04 pg/mL, *P* < 0.001; Fig. 5B) and VIP (0.44 ± 0.03 vs. 0.78 ± 0.08 pg/mL, *P* < 0.001; Fig. 5C) were significantly elevated from baseline following the haze episode, whereas NPY was significantly decreased (6.19 ± 0.73 vs. 2.79 ± 0.42 pg/mL, *P* < 0.001; Fig. 5D).

**Cytokine production of PBMCs is stimulated by PM$_{2.5}$ in vitro**

Of all the cytokines examined, 5 (IL-1β, IL-4, IL-5, IL-8 and IL-10) demonstrated significant increases after PBMCs were exposed to PM$_{2.5}$ to different extents. The production of the Th2 cytokines IL-4 (Fig. 6A) and IL-5 (Fig. 6B) were elevated by incubation with both 0.1 μg/mL PM$_{2.5}$ and 10 μg/mL PM$_{2.5}$, while the proinflammatory cytokines IL-1β (Fig. 6C) and IL-8 (Fig. 6D) and regulatory T cells (Treg) cytokine IL-10 (Fig. 6E) were significantly increased by
Haze Induces Nasal Inflammation

**Fig. 5.** Changes in neuropeptide concentration (pg/mL) in nasal secretions of the participants before and during the haze episode. (A) SP, (B) NGF, (C) VIP and (D) NPY (n=33 for each experiment). SP, substance P; NGF, nerve growth factor; VIP, vasoactive intestinal peptide; NPY, neuropeptide Y.

**Fig. 6.** Concentrations (pg/mL) of inflammatory cytokines in supernatants of peripheral blood mononuclear cells exposed to phosphate-buffered saline (0 mg/mL), 0.1 mg/mL PM$_{2.5}$ or 10 mg/mL PM$_{2.5}$. (A) IL-4, (B) IL-5, (C) IL-1β, (D) IL-8 and (E) IL-10 (n=8 for each experiment). Data on cytokines (IL-13, IL-17A, IL-33, eotaxin, transforming growth factor-βs and IFN-γ), which were not significantly affected by different doses of PM$_{2.5}$, were not provided here. IL, interleukin; IFN, interferon; NS, not significant.

*P < 0.05, **P < 0.01, ***P < 0.001.
incubation with 10 μg/mL PM$_{2.5}$. The production of the Th1 cytokine IFN-γ (Fig. 6F) was not significantly altered by incubation with either 0.1 μg/mL PM$_{2.5}$ or 10 μg/mL PM$_{2.5}$.

**DISCUSSION**

During the study, Beijing was experiencing haze episode with daily average ambient PM$_{2.5}$ concentration of 193.0 ± 30.2 µg/m$^3$ for 5 consecutive days, which is about 7.7-times higher than the WHO threshold$^{15}$; meanwhile, other ambient pollutants, including PM$_{10}$, SO$_2$, CO, NO$_2$ and O$_3$, were increased in parallel (Fig. 1). Our study demonstrated that during the haze episode 75.8% (25/33) of the participants experienced mild nasal symptoms, especially nasal congestion, which is consistent with increased NAR and decreased MCA, compared to the baseline visit before the haze episode. These alterations might be explained by mucosal swelling resulting from ambient pollutant-induced nasal inflammatory response and fluctuation in neuropeptides. In accordance with these findings, Krämer *et al.*$^{13}$ have reported that there is a significant relationship among prolonged exposure to air pollution (using individual annual mean NO$_2$ level), atopic complaints (such as high fever, symptoms of allergic rhinitis and wheezing) and sensitization to pollen/HDM, in a random population.

The fractional concentration of fractioned eNO (FeNO) has been validated as an important marker for airway inflammation in the past decade.$^{16,17}$ Several environmental studies have shown that increased FeNO levels are associated with increases in a wide range of traffic-related air pollutants.$^{18}$ However, few studies have investigated the effect of air pollution on nNO. Nightingale *et al.*$^{19}$ and Olin *et al.*$^{20}$ had measured nNO in healthy volunteers to assess the acute effects of O$_3$ exposure for 2–4 hours and suggested that nNO was not a useful marker detecting acute ozone-induced effects. In contrast, our study has shown that both eNO and nNO levels were significantly increased during a period of 5-day haze episode. The discordance between findings of previous studies and ours might partly be a consequence of the difference in pollutants exposed (multiple pollutants vs. O$_3$) and time course of exposure (5 days vs. 2–4 hours).

In addition to eNO, levels of inflammatory mediators in nasal secretions reflect the inflammation status of the nasal mucosa and parallel the course of inflammatory conditions.$^{21}$ The present study demonstrated that exposure to haze for 5 days resulted in significant increases in the levels of eotaxin, CCL17, IL-5 and IL-8, and attenuated production of the Th1-type cytokine IFN-γ. The association between increase in IL-8 and PM/NO$_x$ has been reported in several studies measuring nasal biomarkers in nasal lavage.$^{22-24}$ Exposure to diesel exhaust particles has also been shown to significantly increase IL-8 expression in primary human bronchial epithelial cell cultures.$^{25}$ However, the up-regulation of eotaxin, CCL17 and IL-5 as well as the down-regulation of TGF-β, IL-10 and IFN-γ in the present study indicates substantial Th2 cell involvement. Considering that previous studies have suggested that diesel exhaust particles may act to enhance immunoglobulin E-mediated aeroallergen sensitization and Th2-directed cytokine responses,$^{26}$ our data indicated that short-term haze exposure may promote Th2-cell polarization and activation in the nasal mucosa of healthy individuals, leading to inflammation and lowered nasal patency. Indeed, attenuated release of TGF-β and IL-10 by haze exposure demonstrated in the present study may also be of consequence, since secretion of TGF-β and IL-10 by Treg cells results in the inhibition of pro-inflammatory cytokine production and the activation of both Th1 and Th2 cells.$^{27,28}$ Thus, it is speculated that haze exposure may reduce the anti-inflammatory function of Treg cells, and
further compounding inflammation in the nose as well as predisposing otherwise healthy individuals to the development of allergic upper airway diseases.

The present study has demonstrated that the levels of the neuropeptide vasodilators SP and VIP were also increased significantly, whereas the levels of the potent vasoconstrictor peptide NPY were decreased significantly, after haze exposure. SP, a neuropeptide of the tachykinin family, exists in type C nociceptive sensory neurons of the human nasal mucosa. There is growing evidence that SP participates in nasal allergic reactions particularly as patients with allergic rhinitis have higher tissue concentrations of SP than healthy individuals and SP induces histamine release from the nasal mucosa. Similarly, VIP, which is released by parasympathetic reflexes, has many functions in the nasal airways, including glandular discharge, vasodilatation and sinusoidal engorgement. The expression of the VIP receptor has also been shown to be higher in the nasal mucosa of allergic rhinitis patients compared to healthy subjects. In contrast, NPY is found in sympathetic neurons, which regulates vasomotor tone in the human nasal mucosa. Taken together, these findings suggest that both increased vasodilation and decreased vasoconstriction by SP, VIP and NPY due to haze pollution possibly exacerbate vasodilation, vascular permeability and glandular secretion, thereby possibly leading to increased nasal congestion and decreased nasal patency.

Similarly, the NGF level in nasal secretion was also increased significantly after haze exposure. NGF is a neurotrophic that is expressed in the glandular, nasal epithelium and peripheral nerves in the nasal mucosa, and has been shown to induce biochemical and structural changes in nerves that can lead to hyperresponsiveness. Animal and human studies have provided evidence indicating that NGF is involved in the pathophysiology of allergic inflammation and neural hyperresponsiveness in the airways. Thus, it is reasonable to presume from the present study that haze-induced increases in NGF may lead to hyperresponsiveness in the nasal mucosa and increase symptoms of sneeze and irritation in the subjects.

PM$_{2.5}$ has been shown to be particles capable of infiltrating into blood stream. De Falco et al. treated PBMCs obtained from unstable Chronic Obstructive Pulmonary Disease patients using combustion-generated ultrafine particles, which induced the release of IL-8 and IL-33. Srivastava et al. argue that expression profiles of genes in PBMCs can be used as a surrogate for monitoring the acute toxicity of fine particulate matter, since responses to diesel exhaust particles exposure are similar between PBMCs and lung tissue. In our in vitro study, the PM$_{2.5}$ induced increase in IL-8 production by PBMCs is consistent with that after haze exposure in vivo and supports a proinflammatory effect of PM$_{2.5}$. However, although haze decreased IL-10 and IFN-γ in nasal secretions, PM$_{2.5}$ increased IL-10 and failed to significantly alter the synthesis and/or release of TGF-β and IFN-γ from PBMCs. This could be a consequence of the difference in the sensitivity to PM$_{2.5}$ of the cells in the nasal epithelium in vivo and the isolated PBMCs in vitro, although this hypothesis needs to be confirmed in future studies. Nevertheless, the result that a PM$_{2.5}$ concentration of as low as 0.1 μg/mL was sufficient to up-regulate expression of IL-4 and IL-5 in PBMCs may be of particular relevance because PM$_{2.5}$ is a chief component of air pollution in Beijing.

In particular, the findings of the in vitro studies assessing the impact of exposure to PM$_{2.5}$ on cytokine secretion by PBMCs are somewhat limited due to the small number of subjects providing PBMCs, which may possibly be the reason for the discrepancy between in vitro and in vivo findings of the present study. In this respect, our study is also limited in that PBMCs,
rather than human nasal epithelial cells, were employed to assess the effects of PM$_{2.5}$. The present study is also somewhat limited in that there is no control group from an area with much lower levels of pollution. Further studies are warranted to examine the effect of PM$_{2.5}$ on nasal epithelial cells obtained from a larger number of subjects selected from a broader population consisting of a mixture of subjects in different age groups and with different comorbidities (e.g. allergic rhinitis) as well as from areas with different pollution levels and meteorological environments.

In conclusion, our results have indicated that a relatively short period of haze exposure with ambient levels of PM$_{2.5}$ above 100 µg/m$^3$ may lead to significant changes in inflammatory cytokines and neuropeptides in nasal secretions of young healthy volunteers. Unlike previous studies focusing on the influence of air pollution on susceptible individuals, our study demonstrated that short-term exposure to severe air pollution resulted in a Th2-polarized inflammation and hypersensitivity of the originally healthy nasal epithelium. Although previous studies have controversial results about the association between air pollution and rhinitis incidence, our data verified that ambient pollutant in Beijing is inflammation-related and helped us better understand the pathogenesis of rhinitis.

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