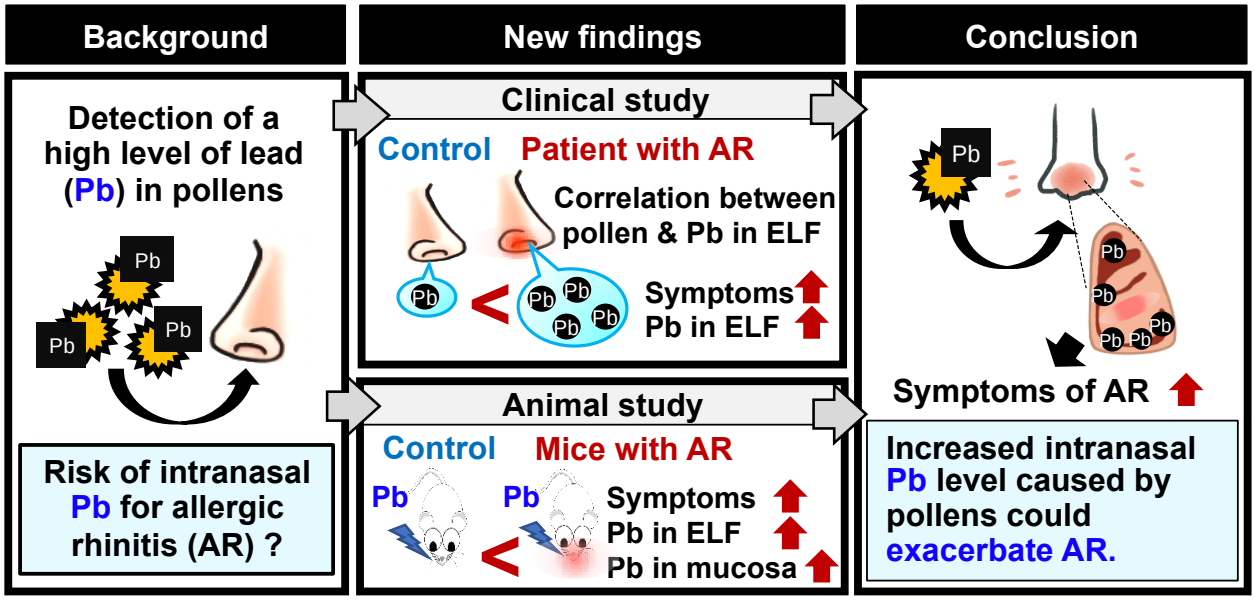
News Release

Title

Intranasal levels of lead as an exacerbation factor for allergic rhinitis in humans and mice

Key Points

- A higher level of lead in nasal epithelial lining fluid (ELF) from patients with pollinosis than that in ELF from control subjects was clinically obtained in season.
- Correlations of lead levels in ELF with pollen counts as well as with severity of subjective symptoms were obtained.
- The clinical results were partially confirmed by our animal study.



Summary

Air pollutants are suspected to affect pathological conditions of allergic rhinitis (AR). After detecting lead (Pb) (375 μg/kg) in Japanese cedar pollen, the effects of intranasal exposure to Pb on symptoms of AR were investigated. Pollen counts, subjective symptoms and Pb levels in nasal epithelial lining fluid (ELF) was investigated in 44 patients with Japanese cedar pollinosis and 57 controls from pre-season to season. Pb levels in ELF from patients were >40% higher than those in ELF from control subjects during the pollen season but not before the pollen season. Pb level in ELF was positively associated with pollen counts for the latest 4 days before visiting a hospital as well as scores of subjective symptoms. Intranasal exposure to Pb exacerbated symptoms in allergic mice, suggesting Pb as an exacerbation factor. Pb levels in ELF and nasal mucosa in Pb-exposed allergic mice were higher than those in Pb-exposed non-allergic mice, despite intranasally challenging the same amount of Pb. Since the increased Pb level in the nasal mucosa of Pb-exposed allergic mice was decreased after washing the nasal cavity, Pb on the surface of but not inside the nasal mucosa may have been a source of

increased Pb level in ELF of allergic mice. Increased nasal Pb level partially derived from pollen could exacerbate subjective symptoms of AR, indicating Pb as a novel hazardous air pollutant for AR.

Research Background

The prevalence of seasonal allergic rhinitis, which is characterized by immunological reactions such as recruitment of eosinophils and release of cytokines, has been rapidly increasing. Seasonal allergic rhinitis has become a global health problem because of its high worldwide prevalence (10-30%). The prevalence of Japanese cedar pollinosis (JCP), a representative seasonal allergic rhinitis in Japan, has reached almost 50%, and JCP is now called a folk disease in Japan.

Health disturbances caused by exposure to various elements including heavy metals have been widely recognized worldwide. In fact, it has been shown that elements modulate immunological and inflammatory reactions. Notably, levels of lead (Pb), cadmium (Cd) and mercury (Hg), which are representative air pollutants, have been reported to increase the risk of bronchial asthma in the general population via modulation of immunological potencies and airflow obstruction. In the context of allergic rhinitis, studies have shown that pollen collected from highly air polluted areas has more allergic potency than that of pollen collected from unpolluted areas. However, there has been no clinical study showing the effects of heavy metals on allergic reaction in the nasal cavity of patients with seasonal allergic rhinitis before the season (pre-season) and during the season (season). Moreover, there has been no experimental study showing effects of intranasal exposure to heavy metals on pathological conditions of allergic rhinitis.

In this study, we first hypothesized that the heavy metals in pollens affect the pathogenesis of JCP. Then a clinical follow-up study was conducted to investigate the contributions of heavy metals to the pathogenesis of seasonal allergic rhinitis under the condition of natural allergen exposure. To provide a more solid basis for a linkage between heavy metals and allergic rhinitis, the results obtained in human subjects were further confirmed by the results of a study using model mice with allergic rhinitis.

Research Results

The Pb levels in ELF from patients were significantly higher than those from controls in season, while the Pb levels in ELF were comparable in patients and control subjects in pre-season (Figure 1). Correlations between each nasal symptom score and Pb levels in human samples from patients in season were next investigated. Spearman's correlation analysis revealed significant associations between Pb levels in ELF and scores for sneezing ($r = 0.22$, $P = 0.026$), nasal blockage ($r = 0.34$, P

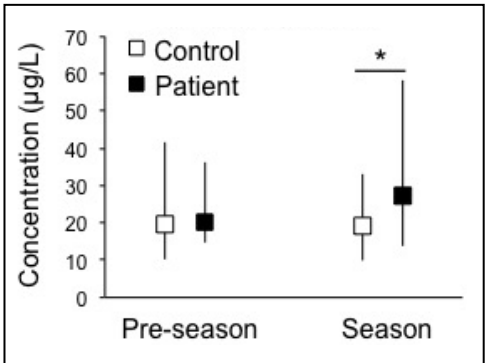


Figure 1. Pb level in ELF.

= 0.001) and total subject symptoms (r = 0.25, P = 0.013), while the score for nasal discharge (r = 0.12, P = 0.252) was not associated with Pb levels in ELF samples. Log-transformed Pb levels in ELF remained positively associated with incidences of sneezing (odds ratio [OR] = 5.27, 95% CI: 1.37~20.28, P = 0.016), nasal blockage (OR = 7.67, 95% CI: 1.69~34.88, P = 0.008) and total subjective symptoms (OR = 7.28, 95% CI: 1.88~28.20, P = 0.004) in multivariable models adjusting for age, sex, BMI, smoking history, sleep time and physical activity (Figure 2). The correlations between the number of Japanese cedar pollen grains and Pb levels in human samples in season were then investigated. There were significant positive correlations between pollen counts for 4 days before visiting a hospital and Pb levels in ELF (Table). This suggest that increased Pb level in ELF is partially derived from pollen.

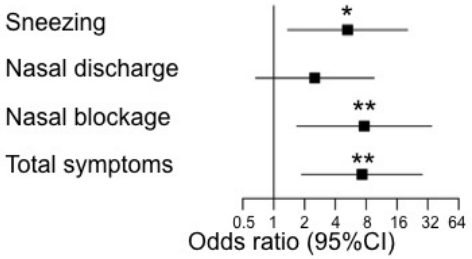


Figure 2. Correlations of nasal symptoms and Pb level in ELF.

Time lag	β	95% CI	P-Value
9 days	-0.04	(-0.09, 0.01)	0.116
7 days	-0.06	(-0.12, 3.13)	0.077
5 days	-0.44	(-0.96, 0.07)	0.093
4 days	0.29	(0.03, 0.54)	0.026*
3 days	0.13	(0.03, 0.22)	0.008**
2 days	0.07	(0.02, 0.12)	0.004**
1 day	0.23	(0.01, 0.44)	0.037*
0 day	-0.01	(-0.08, 0.06)	0.833

Table. Correlations between Pb levels in ELF and Japanese cedar pollen counts.

Thus, our clinical study suggests not only a potential source of intranasal Pb but also a potential role of intranasal Pb as an exacerbator for activated allergic rhinitis in season.

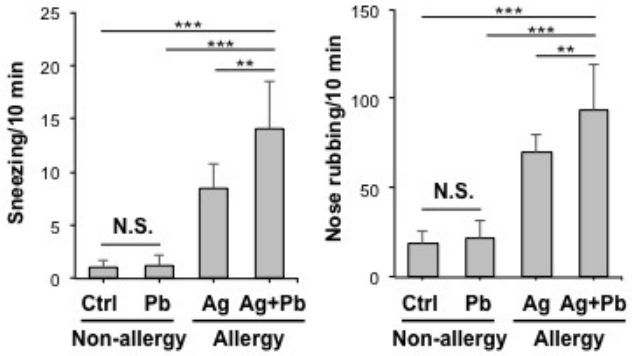


Figure 3. Pb exacerbates nasal symptoms in a mouse model of allergic rhinitis.

In order to confirm the results of our clinical study, animal studies using mice with allergic rhinitis and mice without allergic rhinitis were conducted with or without nasal challenge of Pb and/or the antigen. Levels of symptoms (sneezing and nose rubbing) in mice without allergic rhinitis just after nasal challenge of Pb were comparable to those just after nasal challenge of the solvent of Pb (control). However, those in mice with allergic rhinitis just after nasal challenge of the antigen and Pb were significantly higher than those just after nasal challenge of the antigen, indicating that nasal exposure to Pb exacerbated nasal symptom of the mice with allergic rhinitis (Figure 3).

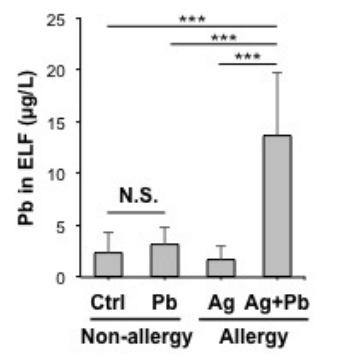


Figure 4. Pb level in ELF from mouse model.

In control mice without allergic rhinitis, Pb level in ELF 24 hours after the nasal challenge of Pb was comparable to that 24 hours after the nasal challenge of the solvent of Pb. In mice with

allergic rhinitis, the mean level of Pb 24 hours after nasal challenge of the antigen plus Pb was 8.4-fold higher than those 24 hours after nasal challenge of the antigen (Figure 4). More importantly, the mean level of Pb in ELF from mice with allergic rhinitis 24 hours after nasal challenge of the antigen plus Pb was 4.3-fold higher than that in ELF from control mice without allergic rhinitis 24 hours after nasal challenge of Pb (Figure 4). Correspondingly, the Pb level in nasal mucosa from mice with allergic rhinitis 24 hours after nasal challenge of the antigen plus Pb was higher than that nasal mucosa from mice without allergic rhinitis 24 hours after nasal challenge of Pb in the condition before washing their nasal cavities (Figure 5). These results suggest that intranasally challenged Pb remained at a high level in the nasal cavity 24 hours after nasal challenge of Pb in allergic mice but not in non-allergic mice despite the fact that allergic mice and non-allergic mice were intranasally exposed to the same amounts of Pb.

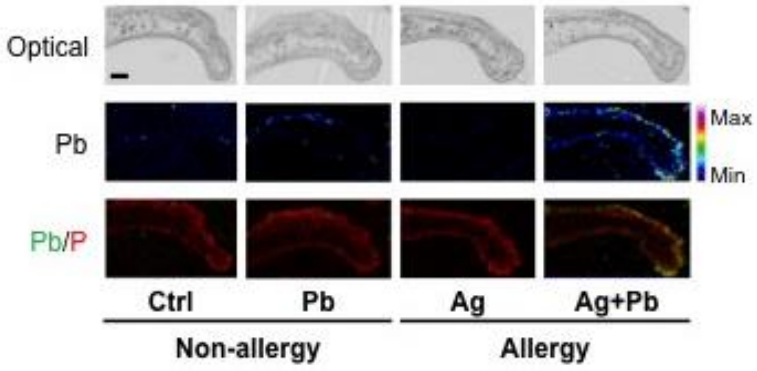


Figure 5. Distribution of Pb in nasal mucosa

Research Summary and Future Perspective

A contribution of Pb adhering to pollen (an air pollutant) to allergic rhinitis could be a worldwide issue. Further allergotoxicologic studies are needed to clarify the molecular mechanisms of Pb-mediated exacerbation of allergic rhinitis and to qualitatively identify other exacerbation factors for allergic rhinitis.

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