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Review article

Adverse respiratory effects and allergic susceptibility in relation to particulate air pollution: flirting with disaster

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The prevalence of allergic conditions such as asthma, rhinoconjunctivitis and atopic eczema/dermatitis has steadily increased in recent decades. Elicitation of an IgE-mediated allergic trait appears to be determined by the complex interplay of multiple genetic and environmental factors. However, although genetic factors in addition to allergen exposure are important, the observed rise in the prevalence of allergic conditions is likely to be ensuing from modifications occurring in the environment (1–3). The remarkable expansion in motor vehicle traffic and its associated emissions has paralleled the world-wide increase in the prevalence of respiratory tract conditions (4). Over the last 40 years the global vehicular fleet has expanded ten-fold and the number of vehicles are predicted to increase even further over the next 20–30 years (5). Estimates by the United Nations indicate that over 600 million people living in cities and towns world-wide are exposed to unhealthy and dangerous levels of motor vehicle generated air pollutants (6).

Although the health effects of urban air pollution on the respiratory tract has been the focus of much research in recent times, it appears that less attention has been given to the potential role of pollutants emitted from motor vehicle exhausts in the elicitation of allergic conditions. Several laboratory based studies have demonstrated that particulate air pollutants emitted from motor vehicles can induce mucosal inflammation, enhance IgE responses, and heighten airway hyperresponsivenss which could provide an explanation for the increasing prevalence of respiratory symptoms and allergic diseases (7). The present article reviews our current understanding of the mechanisms by which pollutants such as diesel exhaust particles (DEP) enhance the underlying allergic inflammatory response, and the evidence that supports the causative link between particulate air pollution from motor vehicles and increasing allergic diseases. This article will comply with the recently revised nomenclature of allergic disorders proposed by an EAACI task force (8).

Particulate air pollutants and respiratory symptoms: epidemiological evidence

A number of epidemiological studies in several countries support the view that exposure to traffic-related pollutants is associated with a broad spectrum of adverse short-term respiratory effects in vulnerable individuals. Studies in Japan (9–11) have shown that people living close to main roads with heavy traffic suffered more respiratory symptoms and allergies than those living further away. Similar studies carried out in the UK (12) and in the Netherlands (13, 14) reported increased respiratory symptoms and reduced lung function in those children living in close proximity of roads with high traffic intensity, which positively correlated with the levels of particulate matter in the

ambient atmosphere. In general, children living close to main roads or in intensely polluted cities suffer greater symptoms of cough and wheeze, show lower lung function measurements, and exhibit increased bronchial hyperresponsiveness (15–18). Brunekreef et al. (19) reported that respiratory symptoms and decreases in lung function measurements in children are strongly correlated with the distance from major motorways. Similar studies carried out in Germany (20, 21), Italy (22) and Japan (23) have shown significant positive association between self-reported truck traffic and self-reported prevalence of wheezing and allergic rhinitis. Unfortunately, reporting biases may be a particular problem with most of these studies.

It appears that asthmatic patients are more vulnerable to the adverse effects of polluted air (24). There is no doubt that particulate air pollutants aggravate asthma. A strong association between increased emergency department visits for asthma and the concentration of airborne particulate matter has been demonstrated in the US (25–27) and in the UK (28). In asthmatic subjects Pope et al. (29) showed that higher levels of particulate matter are negatively associated with changes in peak expiratory flow (PEF) whereas a positive correlation was observed with the use of symptomatic medication. In children with bronchial hyperresponsiveness and high levels of serum total IgE, Boezen et al. (30) demonstrated that the prevalence of respiratory symptoms arised substantially for every 100 $\mu g/m^3$ increase in particulate matter. By using surrogate indicators for traffic-related air pollution it has been demonstrated a significant association between these traffic indicators with adverse respiratory outcomes in children (22, 31). However, other studies have failed to show a clear association between respiratory symptoms and treatment for asthma and proximity of residence to main roads with heavy traffic (32, 33). Limitations in the study design and in the exposure assessment might explain the discrepancies of these findings.

Particulate air pollutants and respiratory symptoms: experimental evidence

The underlying molecular mechanisms that link exposure to traffic-related pollutants to adverse respiratory effects are poorly understood. A number of laboratory studies support the view that some types of ambient air particles elicit inflammatory/irritant responses in a number of resident cell types of the airways, in particular bronchial epithelial cells. In susceptible airways, this may in turn lead to the progression of mucosal inflammation.

Exposure studies with DEP demonstrated a marked infiltration of inflammatory cells, particularly eosinophils, in mice and rabbits (34, 35). Significant inflammatory changes have also been reported in healthy volunteers exposed to DEP (36, 37). In these studies a significant increase in the number of neutrophils and macrophages obtained from bronchial washing and/or bronchoalvolar lavage fluid was observed 6–24 h after exposure.

Airway epithelial cells have been extensively investigated in mechanistic studies of air pollution induced respiratory symptoms due to their distinctive spatial arrangement, predominance in the airways, and their ability of releasing a large number of proinflammatory mediators that help in initiating and maintaining the inflammatory response. When exposed to DEP *in vitro*, human bronchial epithelial cells actively phagocytose these particles and begin to release a number of proinflammatory cytokines such as IL-8, GM-CSF, and sICAM-1 (38). It is of interest that bronchial epithelial cells of asthmatic individuals may be different from those of nonasthmatics with regard to their ability to release different types and quantities of specific inflammatory mediators when exposed to air pollutants. Bayram et al. (39) have recently shown increased sensitivity of asthmatic bronchial epithelial cells, in relation to DEP-induced inflammatory mediator release (IL-8, GM-CSF, and sICAM-1). The finding that DEP can induce release of proinflammatory mediators from bronchial epithelial cells is also in accordance with the findings of Diaz-Sanchez et al. (40), who have investigated the effect of DEP on the synthesis of cytokines in the nasal mucosa of allergic subjects *in vivo*. These authors have shown that intranasal challenge with purified DEP led to increased and readily detectable levels of mRNA for IL-2, IL-4, IL-5, IL-6, IL-10, and IL-13 in the nasal mucosal cells of these individuals 18 h after challenge.

Terada et al. (41) demonstrated that DEPs up-regulate the expression of histamine-1 receptor mRNA in human airway epithelial and endothelial cells, and enhance histamine induced increase in IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF) production *in vitro*. Histamine-1 receptor mRNA is markedly increased in patients with allergic rhinitis (42), and a further up-regulation induced by DEP may further enhance the effects of histamine. Acting via histamine-1 receptors, histamine increases epithelial and capillary endothelial permeability, mucus hypersecretion, airway hyperresponsiveness and smooth muscle contraction, and enhances mediator and cytokine release (43). Similarly, extracts from DEPs have been shown (44) to enhance human eosinophil degranulation and adhesion to nasal epithelial cells. Because eosinophil degranulation is associated with the release of mediators that promote allergic inflammation, this suggests that DEPs can promote eosinophil-mediated hypersensitivity. Peripheral blood mononuclear cells obtained from patients who are allergic to dust mites, when cocultured with DEPs and dust mite

allergens, show increased production of the chemokines IL-8, RANTES and tumor necrosis factor α (TNF-α) in a dose-related and synergistic manner (45). Taken together these studies indicate that particulate pollutants from motor vehicles may have an important proinflammatory effect in the airways.

In an attempt to better define the molecular mechanisms of the effect of DEP on cytokine production, Takizawa et al. (46) have shown that DEP upregulated IL-8 gene expression at the transcriptional level in a human bronchial epithelial cell line *in vitro* by activation of the transcription factor as nuclear factor-κB (NF-κB). The enhancement of allergic inflammation by DEPs has also been suggested to be indirectly mediated by reactive oxygen species (ROS). Generation of ROS after particle inhalation activates redox-sensitive transcription factors such as NF-κB and activator protein-1 by inducing phosphorylation of IκB and generation of c-fos and c-jun (47). It has been recently demonstrated (48) that particulate matter causes a seven-fold increase in NF-κB activation in human airway epithelial cells through an oxidant mechanism. In addition to generating ROS, polyaromatic hydrocarbons derived from diesel exhaust have been shown (49) to trigger cell metabolism via a direct interaction with polyaromatic hydrocarbon cytosolic receptors such as arylhydrocarbon receptor, which can translocate to the nucleus and act as a transcription factor, leading to induction of promoters of metabolizing enzymes or activation of activator protein-1 or NF-κB.

Particulate air pollutants and allergic susceptibility: epidemiological evidence

With regard to the development of allergic sensitization, the epidemiological evidence of a putative link with particulate exposure is less abundant. Environmental factors must be important, as it is indicated by the demonstration of substantial differences in the prevalence of atopy between populations living in urban and rural areas (50–52). Most recently epidemiological comparisons of the prevalence of atopic diseases have also shown marked differences in the prevalence of hay fever and positive skin-tests to common allergens between former West and East Germany (53, 54), and between Hong Kong and China (55). It is possible that tangible differences in air pollution from automobile exhaust in these countries may account for the observed increased prevalence of atopy. Car ownership in the former East Germany is currently rising (56), and a predictable increase in the levels of particulate air pollutants from motor vehicles is to be expected. The rising levels of these pollutants in cities such as Leipzig (formerly in East Germany) since the German reunification has paralleled the marked increase in the prevalence of hay fever and childhood atopy (57). These findings may suggest a causative link between the rising levels of particulate environmental pollution from motor vehicles and the increase in the prevalence of atopy.

Although road traffic pollution from automobile exhausts may be indicated as a risk factor for atopic sensitization, there is little published evidence supporting this view. Some epidemiological studies have reported a clear association between the prevalence of allergy and road traffic-related air pollution (9, 16, 22, 58, 59). We have recently reported an increase in the proportion of positive cutaneous IgE-mediated responses in 234 traffic wardens with a well defined occupational history of road traffic fume exposure in the city of Catania which has one of the highest levels of traffic intensity in Italy (60). In contrast, such differences were not observed in other studies (61, 62). However these studies refer exclusively to gaseous air pollution and not to particulate pollutants; there is no experimental evidence that gaseous air pollutants are able to enhance IgE production or atopic sensitization. In addition, since exposure to ambient particles are substantially different in urban environments throughout the world, it is possible that qualitative rather than quantitative variations in particulate air pollution at different locations may explain differences in prevalence or severity of respiratory allergies.

Particulate air pollutants and allergic susceptibility: experimental evidence

Epidemiological studies have clearly shown a consistent and significant association between ambient levels of various air pollutants and increasing incidence of allergic airway diseases. The marked consistency of this association across different geographic locations of the world after controlling for all potential confounding factors argues for a causal relationship. More recently, these epidemiological studies have been complemented by experimental work in animals and humans. These studies in humans and animals have demonstrated that particulate toxic pollutants, particularly DEP, are able to boost allergic immune responses. Intranasal inoculation of DEP has been reported to have an adjuvant activity for IgE production in mice (63). In the same animal model, coadministration of DEP with antigen has been shown to significantly increase the levels of the Th2 cytokines IL-4, IL-5 (64, 65) and decrease the levels of the Th1 cytokine IFN-γ (66) in the lymph nodes, compared with instillation of antigen alone. The carbon core of DEP contains a number of polyaromatic hydrocarbons (PAH) including anthracene, fluoranthrene, pyrene, and phenanthrene. These major chemical components of DEP exert a number of immunological effects with a significant increase in

IgE production associated with greater εRNA transcription (67–69). In mice immunized intranasally with mite allergen, DEP exerts a specific adjuvant activity in the production of IgE and IgG1 antibodies against *Dermatophagoides farinae* (70).

Most *in vivo* studies in man have looked into the effects of DEPs on the nasal mucosa. Nasal instillation of DEPs in atopic human subjects has been shown to be associated with a 25-fold increase in IgE mRNA and a five-fold increase in IgE levels in nasal lavage (71). DEPs induce proliferation of IgE secreting B cells as well as *in vivo* IgE isotype switch, thereby eliciting both a quantitative and qualitative increase in IgE production (68, 71, 72). Instillation of DEP with ragweed in ragweed atopic subjects induces more than a 50-fold increase in the allergen specific IgE levels increased compared to instillation of either ragweed or DEP challenge alone (40). This was also associated with increased expression of mRNA for the cytokines IL-4, IL-5, IL-6, IL-10 and IL-13, and reduced expression of IFN-γ mRNA production, suggesting that increased IgE production following DEP exposure is associated with the up-regulation of Th2 specific cytokines. Peripheral blood mononuclear cells obtained from atopic subjects and cultured with DEP *in vitro* have been shown to increase IgE secretion and the number of IgE secreting B cells (73). Although these studies demonstrated that DEPs can strongly enhance mucosal allergic inflammation and specific Ig responses in already sensitized subjects, it is not known whether exposure to DEPs may lead to the induction of primary sensitization to a neoantigen. Using a model of nasal challenges, Diaz-Sanchez et al. (74) have shown that coexposure of DEPs together with the neoantigen keyhole limpet hemocyanin (KLH), a glycoprotein isolated from the blood of marine mollusc *(Megathura crenulata),* elicited an IgE anti-KLH response in man.

Conclusions

Taken together the findings of these epidemiological and laboratory based studies support the opinion that persistent exposure to particulate air pollutants from motor vehicles may account for the sharp increase in the prevalence of respiratory symptoms and allergic diseases. In particular the critical rise in DEP and similar airborne materials in urban settings with high levels of traffic intensity may induce in individuals with the appropriate genetic predisposition sensitization to allergens to which they may not otherwise have become sensitized. With the view that particulate air pollutants may differ qualitatively in relation to the initiation of inflammatory and allergic responses, it is crucial to better characterize their biological effects and to incorporate these notions in well-designed epidemiological studies. As soon as pollutants that significantly enhance the airway inflammatory and allergic antibody responses will be better identified, it will be possible to develop appropriate health policies in order to effectively reduce the levels of these compounds in our cities.

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