The Effect of Air Pollution on Asthma and Allergy

Marc A. Riedl, MD, MS

Corresponding author
Marc A. Riedl, MD, MS
Section of Clinical Immunology and Allergy, Division of Pulmonary and Critical Care Medicine, UCLA—David Geffen School of Medicine, 10833 Le Conte Avenue, 37-131 CHS, Los Angeles, CA 90095, USA.
E-mail: mriedl@mednet.ucla.edu

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Air pollution exposure is associated with increased asthma and allergy morbidity and is a suspected contributor to the increasing prevalence of allergic conditions. Observational studies continue to strengthen the association between air pollution and allergic respiratory disease, whereas recent mechanistic studies have defined the prominent role of oxidative stress in the proallergic immunologic effects of particulate and gaseous pollutants. The identification of common genetic polymorphisms in key cytoprotective responses to oxidative stress has highlighted the importance of individual host susceptibility to pollutant-induced inflammation. Future therapy to reduce the adverse effects of air pollution on allergic respiratory disease will likely depend on targeting susceptible populations for treatment that reduces oxidative stress, potentially through enhancement of phase 2 enzymes or other antioxidant defenses.

Introduction

The adverse health effects of air pollutants have been an issue of increasing concern during the past century. The prevalence of allergic conditions such as asthma and allergic rhinitis has increased in parallel with the emergence of global industrialization and resultant dramatic increases in anthropogenic air pollutants. Recent data on asthma prevalence rates support a sharp increase across the globe, with the most dramatic increases appearing in urbanized societies [1]. The underlying reasons for the observed increases in allergic conditions in past decades are undoubtedly complex and multifactorial; however, compelling evidence exists that air pollutant exposure is a primary driving factor. This review summarizes the current understanding of the proallergic effects of air pollutants, especially particulate matter (PM). We provide an overview of recent work investigating the underlying mechanisms, host susceptibility, and therapeutic implications of air pollutant effects on the development and exacerbation of allergic respiratory conditions.

Epidemiology of Air Pollutants and Allergy

Air pollutants originate from anthropogenic and natural sources including motor vehicles, industrial manufacturing, agricultural activities, and wildfires. The combustion of fossil fuels is responsible for the majority of airborne pollutants: nitrogen oxides (NO_2), carbon monoxide (CO), sulfur dioxides (SO_2), and PM. Environmental tobacco smoke (ETS) and ozone, which is produced by atmospheric reactions of NO_2, hydrocarbons, and ultraviolet light, are additional air pollutants with significant health effects. Of the common air pollutants, PM has been studied in the greatest detail due to significant and increasing production by motor vehicles. The largest single source of airborne PM from motor vehicles is derived from diesel exhaust. Diesel fuel combustion results in the production of diesel exhaust particles (up to 100 times more particles than gasoline engines) and gaseous compounds such as NO_2 and hydrocarbon precursors of ozone. Diesel engine use has increased in many parts of the world due to superior energy efficiency and durability. Thus, diesel exhaust particles (DEP) are a predominant and representative particulate pollutant widely used to study the effects of PM. Accurate measurements of human in vivo ambient exposure to pollutants have proved challenging. Exposure to automobile traffic is often used as a proxy for particulate air pollution exposure in observational studies. It is generally believed that ambient exposure to DEP is related to proximity of high vehicular traffic. Thus, DEP levels are generally much higher in urban than rural areas. Ambient exposure has been quantified and demonstrated to achieve levels at which in vitro studies show significant physiologic effects [2].

The impact of air pollution on respiratory health has been described in numerous epidemiologic investigations [3]. Increased symptoms of cough, bronchitis, asthma, and chronic obstructive pulmonary disease have been associated with elevated air pollutant levels. Recent data

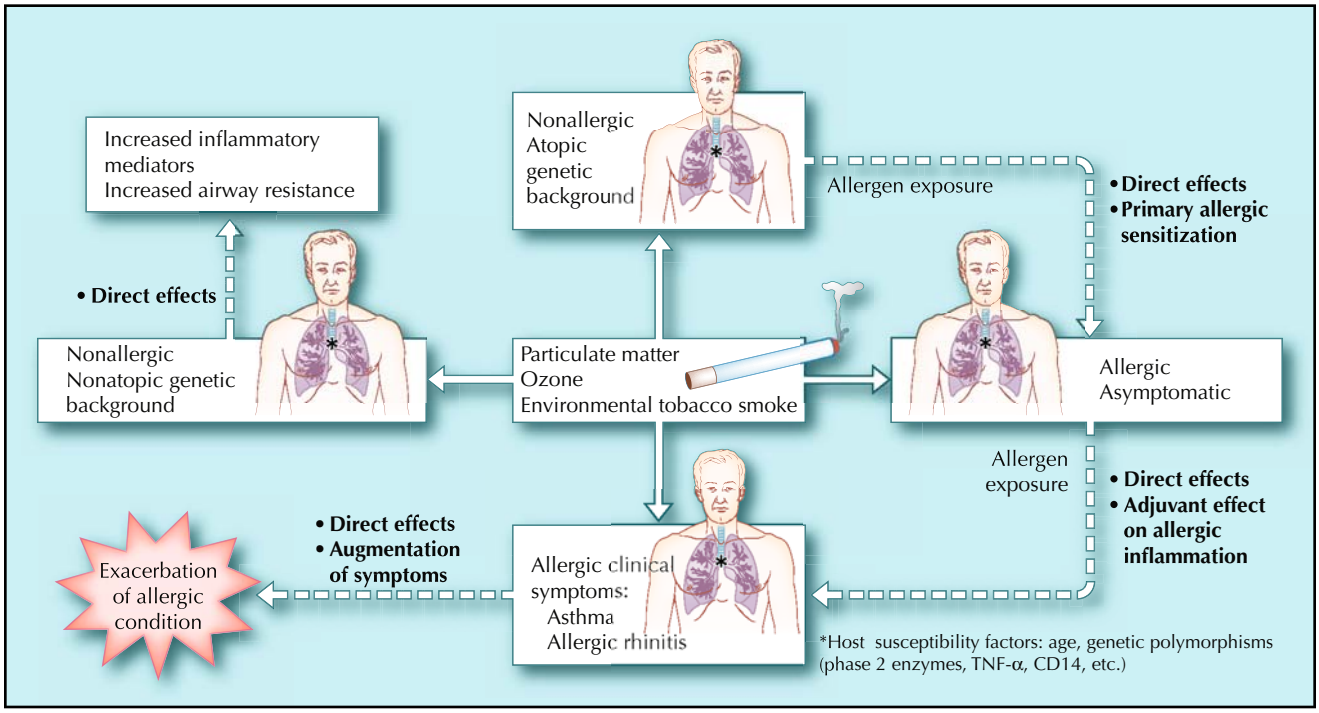

Figure 1. Conceptual summary of potential clinical effects of air pollution on allergic respiratory conditions based on current experimental data. Outcome of pollutant exposure (*along dashed arrows*) is dependent on factors including genetic background, host susceptibility to oxidative stress, and duration/intensity of pollutant exposure. With significant exposure, direct effects of air pollutants are likely to be observed in most persons; however, atopic individuals are at additional risk due to the adjuvant effects on allergic inflammation.

from Gauderman et al. [4] suggest that current levels of urban air pollution may have lasting adverse effects on lung development in children from age 10 to 18 years, as measured by forced expiratory volume in 1 second (FEV_1). With regard to atopic disease, many observational studies support a link between air pollution and asthma. Increased asthma prevalence is observed in urban polluted environments, and the rising incidence of new asthma cases has been associated with long-term increases in total suspended particle levels [5]. Countries with recent rapid industrial development have witnessed sharp increases in asthma prevalence. For instance, asthma cases in China have risen an estimated 40% in the past 5 years concurrent with rapid increases in urban air pollution [6]. Air pollutant effects appear to increase acute asthma exacerbations, medication use, and hospitalization [7]. The association of asthma with chronic exposure to motor vehicle traffic is well-described in the pediatric population. Recent work by McConnell et al. [8] showed strong associations of pediatric asthma medication use, wheeze, and lifetime asthma incidence with living less than 75 m from a major road. ETS exposure is an important factor in asthma exacerbations, particularly in children, because parental smoking is associated with more severe asthma symptoms, increased emergency department visits, and life-threatening attacks [9]. Thus, several air pollutants have been linked to asthma symptoms and severity.

In addition to the direct association with asthma, air pollution exposure has been linked to increased rates of allergic sensitization [10]. Many studies suggest atopic conditions are more common in urban than in rural settings. A large health survey demonstrated a higher prevalence of positive skin tests in individuals living in urban compared with rural communities in the United States [11]. This trend for greater atopy in urban versus rural populations also has been seen in several European countries. A large pediatric study in France reported increased odds of atopy with increasing 3-year averaged local concentration of ozone, SO_2, NO_2, and particles with diameter of 10 μm or less (PM10) [12]. These findings suggest but do not prove a causative link between the rising levels of air pollution and the increasing prevalence of atopy.

Pro-allergic Effects of Air Pollutants

In vitro, animal, and human experiments have demonstrated important biologic effects of air pollutants with regard to the development and exacerbation of allergic conditions. Individual pollutants have been studied to varying degrees; however, a general mechanistic commonality exists, in that most airborne pollutants skew the immune response toward a T-helper (Th) type 2–like phenotype. DEP has been studied the most extensively as a model particulate pollutant. Currently, experimental data support four important biologic effects of DEP, illustrating pathways by which air pollutants may promote the development of allergy respiratory inflammation (Fig. 1). 1) DEP exposure directly induces increased inflammatory

mediator expression, including histamine and cytokines, and increases inflammatory cells in bronchial tissue and the systemic circulation. 2) DEP exposure increases airway hyperresponsiveness in patients with asthma. 3) DEP exposure with allergen increases immunoglobulin (Ig) E and cytokine responses compared with allergen exposure alone in sensitized individuals. 4) DEP exposure with allergen increases the rate of primary allergic sensitization to allergen compared with allergen exposure alone in atopic individuals.

DEP appears to have direct inflammatory effects including mast cell and basophil activation [13]. Increased histamine levels are seen in the bronchoalveolar lavage (BAL) fluid of healthy individuals exposed to DEP. Short-term exposure of healthy human subjects to diesel exhaust at high concentrations induces strong inflammatory responses. In controlled chamber exposure experiments, DEP increases circulating neutrophils and platelets, sputum neutrophil counts, bronchial tissue mast cells, neutrophils, and lymphocytes. In addition, interleukin (IL)-6 and IL-8 expression is increased, as is expression of intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 [14]. In patients with mild asthma, DEP exposure increases airway resistance and hyperresponsiveness to methacholine [15]. Notably, human exposures to ozone induce similar increases in BAL fluid inflammatory cells, cytokines, and airway hyperresponsiveness.

Investigations with DEP have reproducibly demonstrated profound adjuvant effects on the initiation and intensity of allergic inflammation when DEP is given concomitantly with allergen exposure. In vitro studies with DEP show proinflammatory effects at several important steps of the allergic cascade. Human B cells cultured with IL-4 and CD40 monoclonal antibodies in the presence of DEP-derived polyaromatic hydrocarbons (PAH) demonstrate up to a 360% increase in IgE production [16]. In addition, peripheral blood mononuclear cells from allergic subjects co-cultured with DEP and allergen show synergistic increases in IL-8, released on activation, normal T-cell expressed and secreted (RANTES), and tumor necrosis factor (TNF)-α production [17]. These cytokines are overexpressed in asthmatic BAL fluids and are believed to enhance airway inflammatory responses. In vitro studies also suggest that bronchial epithelial cells are profoundly affected by DEP exposure, particularly in asthmatic individuals. Cultured bronchial epithelial cells from asthmatic patients constitutively release greater amounts of IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), RANTES, and soluble ICAM-1 compared with nonasthmatic individuals. Exposure to low DEP concentrations (10 μg/mL) significantly increase release of these cytokines from asthmatic bronchial epithelial cells, whereas nonasthmatic bronchial epithelial cells require higher concentrations of DEP (50–100 μg/mL) to cause significant increases in IL-8 and GM-CSF production [18].

Animal studies have demonstrated an increase in total and antigen-specific IgE and increases in IL-4, IL-5, and GM-CSF in response to DEP exposure [19]. Human studies on DEP effects have confirmed increased IgE isotope switching in vivo resulting in elevated total and allergen-specific IgE [20]. Chemokine, cytokine, and histamine release in response to allergen is upregulated by DEP nasal exposure in humans. This has been aptly demonstrated in dust mite–sensitive subjects challenged intranasally with allergen alone or DEP followed by allergen [21]. Compared with dust mite allergen alone, only 20% of the amount of intranasal dust mite allergen is required to produce symptoms if given with DEP. Thus, exposure to DEP may convert asymptomatic atopic individuals to symptomatic by increased histamine release and receptor expression, and by lowering the allergen threshold necessary to produce symptoms. Gaseous pollutants may also modify responses to allergen, though fewer studies have been performed. Animal studies with ozone, SO_2, and NO_2 exposures show augmented allergic antibody production and pulmonary inflammation after allergen challenge. Human exposure studies with ozone demonstrate increased bronchoconstrictive and eosinophil response to inhaled allergen after ozone pre-exposure [22].

Further experimental evidence supports the capacity of air pollutants to drive a de novo mucosal IgE response to a neoantigen (ie, increase the rate of primary allergic sensitization) [23]. Animal studies have shown ozone, SO_2, NO_2, ETS, and DEP to effectively increase allergic respiratory sensitization to ovalbumin. In experimental human models, nasal exposure to keyhole limpet hemocyanin (KLH) alone induces an antigen-specific IgG response in atopic individuals, whereas identical intranasal exposure with concomitant intranasal DEP induces a robust KLH-specific IgE response. The human subjects in this experiment were skin-test positive to at least one common aeroallergen, thus identifying atopic individuals. Whether exposure to DEP can make a nonatopic person become atopic is unproven. However, these results suggest that pollutant exposure can induce allergic sensitization to an allergen to which an atopic individual normally would not be sensitized. Though it is ethically prohibitive to replicate such human experiments with "real-world" allergens, this effect may be a significant factor in the growing prevalence of allergic sensitization as demonstrated in recent longitudinal surveys [24]. These findings are likely of great clinical relevance, because more than 76 million individuals in the United States alone reside in areas with significant ambient PM exposure [25]. In these environments, atopic individuals are consistently exposed to respiratory allergens in conjunction with PM and other pollutants.

Air pollution contributes to allergic disease in other "indirect" ways. Global climate changes due to increased levels of CO_2 and other "greenhouse gases" have a profound effect on vegetation growth and pollen production. A recent study on ragweed plants showed that "urban"

plants growing in areas with increased CO_2 exposure grew three to five times larger and produced 10 times more pollen than "rural" plants with less CO_2 exposure [26]. Warmer climates also extend the growing season with earlier and prolonged pollen release by plants. DEP may also physically increase the allergen dose that reaches the lungs because DEP have been shown to adsorb antigens onto their surface and may act as carriers of allergens into the respiratory tract.

Molecular Mechanisms of Pollutant Proallergic Effects

With widespread recognition that air pollution is important in the pathogenesis and exacerbation of allergic respiratory disease, considerable work has investigated the molecular mechanisms underlying these effects. Substantial evidence implicates cellular oxidative stress as a primary factor in the biologic effects of air pollutants. Reactive oxygen species (ROS) such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^+) are formed during cellular exposure to a variety of air pollutants: ozone, SO_2, and DEP containing highly reactive chemicals (ie, PAH, quinones) on the surface of carbon-cored particles. ROS deplete cellular antioxidant glutathione stores and react with proteins, lipids, and DNA, leading to cellular damage. The role of oxidative stress in allergy and asthma was the topic of a recent comprehensive review [27].

In vitro, animal, and human studies demonstrate the importance of oxidative stress in mediating the inflammatory and adjuvant effects of DEP. Tissue culture macrophages and bronchial epithelial cells generate ROS with exposure to DEP or DEP extracts [28]. With the use of in vivo chemiluminescence, H_2O_2 has been identified in the lungs and mediastinal fields of rats exposed to concentrated ambient particles [29]. To date, in vivo human studies have shown indirect evidence of ROS production with DEP exposure. Controlled DEP exposure leads to airway inflammation with increased sputum neutrophils and myeloperoxidase, and increased CO, a sensitive marker of oxidative stress, in exhaled air [30].

Further evidence shows that DEP act as potent activators of transcription factors mitogen-activated protein (MAP) kinase and nuclear factor (NF)-κB [31]. NF-κB activation appears to occur dose-dependently and is capable of inducing gene transcription for a variety of cytokines, chemokines, and adhesion molecules that mediate DEP-induced airway inflammation. This includes the proallergic production of IL-4, IL-5, and IL-13, as well as RANTES, GM-CSF, TNF-α, ICAM-1, and VCAM-1. Notably, DEP-induced NF-κB and MAP kinase activation is inhibited by pretreatment with the thiol antioxidant N-acetylcysteine (NAC) [32], strongly supporting the concept that pathway activation is due to ROS derived from DEP. Low-dose DEP has been shown in vitro to inhibit production of IL-10 from human peripheral blood mononuclear cells [33]. IL-10 is a cytokine critical for the maintenance of tolerance. Murine studies also suggest that DEP inhibit Toll-like receptor (TLR) ligand interferon (IFN)-γ responses by interfering with cytokine signaling pathways that signal natural killer cells to produce IFN-γ. Thus, upregulation of proinflammatory mediators via oxidative stress-induced NF-κB activation in conjunction with inhibition of IFN-γ and IL-10 may contribute to the association between DEP exposure and allergic respiratory disease.

The central role of antigen-presenting cells (APC) in particulate-induced inflammation has also become clearer with recent investigations of dendritic cells (DC). Previous data showed oxidative stress at the APC level favors Th2 skewing of the immune response and suppresses Th1 differentiation. Studies with murine DC now demonstrate that DEP-induced oxidative stress inhibits TLR-induced DC maturation and IL-12 secretion [34••]. This impaired DC function results in decreased IFN-γ in antigen-specific T cells. The net effect may be enhanced Th2 responsiveness to environmental allergens. The effect of oxidative stress on DC function has been confirmed by in vivo murine studies employing glutathione depletion by systemic diethyl maleate [35]. This oxidative stress challenge interferes with IL-12 production and costimulatory receptor expression in DC, and reduces skin IFN-γ production and delayed-type hypersensitivity responses to contact-sensitizing antigens. Such effects are reversed by the glutathione precursor NAC. Thus, oxidative stress regulates immune function of DC with suppression of Th1 immunity, which may allow unopposed Th2 polarization and enhanced allergic inflammatory responses.

Variability of Host Response to Air Pollutant Exposure

A valuable framework for considering host susceptibility to proallergic effects of air pollutants is a hierarchical model of effects based on current mechanistic data [2]. This model emphasizes the concept of redox equilibrium in which ROS induce a range of host cytoprotective responses to prevent cellular injury. ROS production that exceeds cellular antioxidant defenses creates an imbalance resulting in oxidative stress. At low levels of pollutant exposure, a number of protective cellular defenses are active in neutralizing ROS and detoxification of xenobiotics such as air pollutants. Inducible phase 2 metabolizing and antioxidant enzymes such as *NQO1, GSTM1,* and *HO-1* represent an early and sensitive response to oxidative stress. Nrf-2, acting via the antioxidant response element, is a major transcription factor controlling functional phase 2 enzyme expression. Furthermore, as discussed later, genetic polymorphisms for phase 2 enzyme expression may confer individual susceptibility to pollutant-induced oxidative stress. Failure of these enzymes to neutralize the effects

of ROS due to genetically low levels of enzyme expression or sufficiently large oxidative stress leads to MAP kinase and NF-κB activation with resultant proinflammatory cytokine/chemokine expression. Levels of oxidative stress beyond this stage overwhelm the cytoprotective response and induce cellular apoptosis or necrosis.

Given that the balance between oxidative stress and antioxidant pathways controls the occurrence and level of inflammation, deficiencies in antioxidant defense pathways are expected to increase susceptibility to environmental pollutants that promote oxidative stress and allergic inflammation. Recent investigations have identified examples of this interindividual variability in endogenous responses to pollutant exposure. Human DEP nasal challenge identifies a susceptible subgroup developing an exaggerated nasal inflammatory response both to the particles alone and to a contemporaneously administered allergen [36]. The reproducible interindividual variability has been closely linked to *GSTM1* and *GSTP1* polymorphisms. Perhaps not surprisingly, these genetic polymorphisms of antioxidant enzymes have also been identified as possible risk factors in the development of asthma. For instance, *GSTM1*-null individuals have a 3.5-fold increased risk for asthma compared with individuals who have functional *GSTM1* genotypes. *GSTP1* (Val105/Val105) individuals have sixfold reduced risk of asthma compared with *GSTP1* (Ile105/Ile105) individuals. Conceivably, the asthma risk identified by such polymorphisms primarily represents susceptibility to the harmful respiratory effects of particulate air pollution.

Genetically determined host response to oxidative stress is an expanding area of research. Recent work has further described associations of glutathione S-transferases (GST) polymorphisms with asthma phenotype and with inflammatory responses to particulates and ozone. Two independent case-control groups in a Japanese population describe association of the *GSTP1* Ile105Val polymorphism with asthma [37]. Further analysis revealed this association was only significant for *GSTM1*-positive genotypes, highlighting the potential complex gene-gene-environment interactions of asthma. Investigation of *GSTM1* and *GSTP1* polymorphisms in asthmatic children exposed to ozone showed increased respiratory symptoms in children with *GSTM1*-null or *GSTP1* Val/Val genotypes [38]. In children with both genotypes, the respiratory difficulties were even greater. Ragweed allergen–sensitive subjects with *GSTM1*-null genotype have greater nasal IgE responses than *GTSM1*-positive subjects when exposed to ragweed allergen with ETS exposure [39••]. Enhancement of nasal IgE and histamine response is greatest in subjects with both *GSTM1*-null and *GSTP* Ile105 genotypes. Notably, *GSTM1*-null and *GSTP1* Ile105 polymorphisms are present in approximately 50% and 40% of the population, respectively, making the public health impact of these factors quite significant. CD14 +1437GG or GC genotype appears to be a risk factor for asthma severity in Latinos with asthma who are exposed to ETS [40•]. Polymorphisms in TNF-α may be an important determinant in lung function responses to ozone exposure [41].

Additional work is necessary to further define genotype-phenotype associations and to investigate the complex gene-gene-environment interactions undoubtedly involved in the host response to environmental air pollutants. Ultimately, prospective identification of individuals susceptible to the detrimental respiratory effects of air pollutants may be possible. This variability in susceptibility may be one plausible explanation for previous equivocal studies of antioxidant therapy for asthma in the general population. Identifying susceptible subpopulations will be a vital component of study design for future investigations of antioxidant therapy in allergic conditions, but may pose ethical issues in the work place.

Therapeutic Implications

Collectively, this knowledge provides the opportunity for intervention and potential prevention of pollutant-induced health complications. In this regard, three major areas of focus should be considered. The most direct approach to addressing air pollutant health effects is to reduce exposure through regulatory actions. Laws governing the production of harmful air pollutants should reflect the known health risks of human exposure. Clinicians and scientists should be integrally involved in these matters of public policy and governmental legislation. Current regulations have been successful in improving some measures of air quality. However, existing policies have little impact on certain important measures of air pollution, such as ultrafine particles (≤ 0.1 μm). The US Environmental Protection Agency has established regulatory standards for ambient PM10 and PM2.5, based on data supporting the adverse health effects of these particles. Less is known about the health effects of more abundant ultrafine particles, for which no regulatory standards currently exist. Recent data suggest ultrafine particles have greater PAH content and exert greater biologic effects than coarse or fine particles. As our understanding of the health effects of specific pollutants increases, corresponding regulatory measures will be vital to public health. Additionally, identifying suitable clinical markers for human pollutant exposure and oxidative stress will allow better assessment of air quality policy effectiveness.

Secondly, as unhealthy pollutant exposure is likely to continue for the foreseeable future, the identification of populations susceptible to pollutant-induced inflammation will be an important component of evaluation and risk stratification. This is particularly relevant to individuals with atopy and asthma, as evidence accumulates supporting the adjuvant effects of pollutants on the development and exacerbation of allergic conditions. Interventions to reduce pollutant effects in this susceptible population will

provide a prime opportunity to favorably impact pollutant-associated morbidity.

Finally, the development of therapeutic interventions for pollution-susceptible populations is an area of ongoing research. At present, the effects of commonly used inhaled or intranasal corticosteroids on pollutant-induced inflammation are unclear. Glucocorticoids inhibit transcription factors for inflammatory cytokines, but may similarly prevent transcription of antioxidant enzymes and other protective factors. Further, ROS may inactivate histone deacetylase-2, a factor required for corticosteroid inhibition of the inflammatory response. A study of serum lipid peroxide levels in asthmatic patients well-controlled on inhaled corticosteroids and long-acting β_2-agonists for 3 months showed mean lipid peroxide concentrations remained significantly higher in asthmatics compared with healthy controls [42]. Inhaled budesonide for 4 weeks in patients with mild asthma failed to prevent the functional response (reduced FEV_1, increase in symptom score) to ozone exposure, though sputum neutrophil and IL-8 concentrations were reduced [43]. Moreover, although some human studies suggest that topical corticosteroids blunt the inflammatory respiratory effects of NO_2 [44], others have shown intranasal steroids to be ineffective in preventing the proinflammatory effects of DEP intranasal exposure [45]. Thus, current standard treatment may not adequately address respiratory oxidative stress burden induced by air pollutant exposure.

There is considerable interest in identifying methods to enhance the antioxidant defenses of the human airway. To date, antioxidant therapy for human asthma has been generally disappointing, as evidenced by the lack of clinical effect seen with various antioxidant regimens. However, the discovery of individual genotypic susceptibility to pollutant-induced oxidative stress may allow more focused investigation of such therapies in a selected population. A report describing the beneficial effects of dietary antioxidant supplementation among genetically susceptible children in a highly polluted environment suggests such strategies may be effective [46].

Promising approaches aimed at reducing pollutant-induced cellular oxidative stress have recently emerged. Therapy directed at up-regulating phase 2 enzyme gene expression via the Nrf-2 signaling pathway may be useful in offsetting the inflammatory effects of pollutant-induced ROS. The Nrf-2 signaling pathway is a negative regulator of inflammation through induction of more than 200 antioxidant, cytoprotective, and detoxification enzymes. The identification of potent oral Nrf2-activators, such as sulforaphane (SFN) found in cruciferous vegetables, has further facilitated development of this therapeutic approach. Recent investigations show this gene-based strategy to be effective in blocking the proallergic effects of DEP on human B-cells because DEP-induced IgE enhancement is inhibited by preculture with SFN [47•]. Additional studies using human bronchial epithelial cells confirm this strategy to be effective in protecting against DEP extract oxidative effects [48••]. SFN effectively up-regulates phase 2 enzyme expression (GSTM1, NQO1) and blocks DEP extract–induced IL-8, GM-CSF, and IL-1β production by human bronchial epithelial cells. Recent in vivo human studies have confirmed that oral SFN from cruciferous vegetables significantly induces nasal phase 2 enzyme expression (Riedl, Diaz-Sanchez, unpublished data). Ongoing human studies will evaluate the efficacy of this strategy in protecting against DEP-induced respiratory inflammation.

Thiol antioxidants (eg, NAC and bucillamine) represent another logical therapeutic strategy to reduce pollutant-induced oxidative stress. These agents increase glutathione available to scavenge ROS and participate in detoxification and conjugation of xenobiotics. NAC has shown promise in animal studies, but has failed to show significant in vivo protective effects against DEP-induced airway oxidative stress in human studies (Diaz-Sanchez, personal communication). Compared with NAC, bucillamine is a more potent antioxidant because it has two donatable thiol groups for glutathione and concomitant activation of Nrf2. The potential effects of bucillamine on the proallergic effects of DEP or other pollutants have not yet been investigated. Other potential avenues for antioxidant therapy in allergy and asthma are in the early stages of investigation. These include lactoferrin [49] and fullerene nanomaterials [50], both of which show the capacity to abrogate oxidative stress–mediated allergic inflammation in experimental models. Concerted efforts should be made to move such novel approaches toward clinical application.

Conclusions

Current evidence implicates air pollution exposure as a risk factor for the genesis and severity of asthma and upper airway allergic disease. Air pollution may also be contributing to the apparent increased prevalence of atopy, though fewer data on this topic exist. Recent research has elucidated molecular mechanisms by which pollutants exert proallergic effects. As our understanding of individual susceptibility to air pollutant effects evolves, diagnostic screening or profiling can be envisioned as a component of the respiratory evaluation. This would enable specific recommendations based on individual susceptibility and ideally allow effective chemopreventive therapy to reduce pollutant-induced oxidative stress. Whether such chemopreventive strategies will prove clinically useful is not currently known. However, in an approaching age of individualized medicine and increasing urbanization, such an initiative may represent a remarkable opportunity to improve the health of those with allergic respiratory disease and prevent further increases in the burden of atopy.

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