

Pollutants and Asthma: Role of Air Toxics

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Asthma is a disease characterized by intermittent bronchoconstriction due to increased airway reactivity to both allergic and nonallergic stimuli. Most asthma exacerbations that result in hospitalization are associated with viral upper respiratory tract infections. Such infections typically induce T-helper type 1 (T_{H1}) responses in the airway, involving activation of nuclear factor-kappaB (NF-κB). However, a more recently appreciated cause of asthma exacerbation is exposure to pollutants, including ozone and various components of particulate matter (PM), including transition metals, diesel exhaust, and biologicals such as endotoxin. Although the role of air toxics in asthma pathogenesis remains incompletely examined, many components of PM that are active exacerbants of asthma are also prominent air toxics (metal ions and organic residues). These agents have been observed to activate NF-κB. Reviewed in this article are the actions of specific air pollutants on airway inflammation in humans and potential common response pathways for ozone, PM, and several air toxics. *Key words:* air toxics, asthma, exacerbation, T_{H1}, T_{H2}. *Environ Health Perspect* 110(suppl 4):565–568 (2002).

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Asthma is a disease characterized by intermittent bronchoconstriction due to increased airway reactivity to both allergic and nonallergic stimuli. Underlying these phenomena is a chronic, eosinophilic airway inflammation. Perhaps the most common and significant risk factor for development of asthma in children is induction of an immunoglobulin E (IgE; allergic) response against indoor allergens (1,2). However, nonallergic stimuli, which do not directly interact with IgE, are common causes of asthma exacerbation. Asthmatic individuals have been identified as a population that is especially sensitive to the effect of ambient air pollutants. Although pollutants might enhance IgE-mediated chronic inflammation via T-helper type 2 (T_{H2}) processes, they more likely induce exacerbation of asthma. Indeed, many pollutants associated with asthma exacerbation induce neutrophilic inflammation in nonallergic subjects.

Viral infections and pollutants typically induce T_{H1}-type responses in the airway, involving activation of nuclear factor-kappaB (NF-κB). Yet in asthmatic individuals, these processes may also exacerbate eosinophilic inflammation. This observation suggests that chronic allergic airway inflammation may modify the response to nonallergic stimuli, thus magnifying the impact of such agents. The agents more commonly examined for asthma exacerbation are criteria air pollutants, such as ozone and particulate matter (PM). The role of air toxics in asthma has not been vigorously examined, despite the frequency in which they are encountered. However, many of the agents identified in PM can also be considered air toxics and demonstrate that this important class of pollutants likely has a significant impact on asthma. Reviewed in

this article are studies that exemplify the impact of ozone, particulates, and toxic components of particulates on asthma.

Ozone and Asthma

Epidemiologic studies clearly demonstrate that increases in ambient air ozone are linked with increased occurrence of acute asthma exacerbations. Markers for such events, including increased hospitalizations and emergency room visits, are usually noted 24 hr after the increase in inflammation, suggesting that inflammation may play a role in such events (3–8). During the 1996 Summer Olympic games, an effort to decrease automobile traffic in Atlanta, Georgia, resulted in decreases in ambient ozone levels. Asthma exacerbations decreased as well, again demonstrating a link between ambient ozone levels and asthma exacerbations (9).

Exposure to ozone is known to induce increases in airway inflammation (10–12). In asthmatic individuals, the effect of ozone exposure is exaggerated, resulting in either increased neutrophilic inflammation (13–15) or an augmentation of eosinophilic inflammation (16,17). In addition to asthmatic individuals being more sensitive to ozone per se, ozone appears to augment both the immediate and late-phase response to allergens. Initially, Molfino and colleagues (18) described increased sensitivity to inhaled allergen after exposure to a relatively low level of ozone (0.12 ppm for 2 hr). Although other studies examining this dose of ozone do not reveal such an effect (19), higher levels of ozone clearly enhance the immediate effect of inhaled allergen on bronchoconstriction (20,21). Nasal challenge studies also demonstrate that ozone exposure might enhance the

late-phase response to allergen (22,23). Thus, persons with allergic inflammation of the airway are differentially susceptible to the effect of ozone, an agent that in nonallergic subjects induces neutrophilic inflammation (24–26).

Toxic Components of Particulate Matter and Asthma

Particulate matter is an important pollutant and is associated with increased morbidity and mortality (24,27–30). PM is also associated with increased disease severity in asthma (31–33). Indeed, increased admissions to hospital for asthma are linked to increased PM exposure, as are decreased peak flow measurements in children (31,34,35). An interesting study in the Utah Valley, Utah, showed a marked decrease in admissions to hospital for asthma and respiratory tract illnesses when a local steel mill was closed, with subsequent increase in such events when it reopened (32,33).

Although a clear mechanism for the action of PM in asthma exacerbation has not been identified, studies with model pollutants, including residual oil fly ash (ROFA) and Utah Valley dust (UVD) particles, suggest that PM enhances T_{H1}-like, neutrophilic inflammation. Many of the active agents in various PM species also fall into the broad category of air toxics. ROFA is a potent proinflammatory agent that has oxidant activity, likely mediated by vanadium species and nickel (36–40). UVD is another PM in which its biological activity is associated with metal content and oxidant character (41–44). Diesel exhaust particles (DEPs) contain polycyclic aromatic hydrocarbons. Each of these PM components can be considered air toxics. The specific impact of these agents in humans is outlined below.

ROFA particles have been shown *in vitro* to affect prostaglandin metabolism and induce cytokine production in epithelial cells (45–48). Animal studies have also demonstrated that ROFA is associated with increased

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neutrophilic airway inflammation (49). Animal studies also show that ROFA can exacerbate allergic inflammation in mice and that it enhances sensitization to allergens in a rat model (50–52).

UVD has also been shown to induce airway inflammation in animal studies and to induce proinflammatory changes in epithelial cells *in vitro*. Perhaps most intriguing is the decreased effect of UVD particles collected during the time that the local steel mill was closed (44,53,54). In humans, instillation of extracts made from UVD collected during the years the mill was open versus those collected when it was closed was consistent with animal and *in vitro* studies demonstrating that influx of neutrophils was associated with dust collected during active years and was blunted in extracts made from UVD collected during a year the mill was closed (42). Humans exposed to concentrated ambient air particles also show subtle evidence of increased respiratory tract inflammation (43). Thus, it seems clear that PM can induce inflammation, not unlike ozone. This proinflammatory effect of PM may account for its ability to exacerbate asthma.

Diesel exhaust and resultant DEPs are also an interesting component of PM. Human challenge studies with diesel exhaust reveal increases in airway inflammation, including increases in airway neutrophils and mast cells (55–57). Diesel exhaust exposure has been shown to enhance nonspecific airway reactivity in asthmatic individuals as well (58). DEPs, in nasal instillation studies, have been shown to induce increases in total and antigen-specific IgE, increase cellular response to nasally applied allergen, and enhance production of T_H2 cytokines such as interleukin (IL)-4 and IL-13 (59–64). DEPs also enhance sensitization to a neoantigen, keyhole limpet hemocyanin (KLH), such that antigen-specific IgE against KLH is generated (65). *In vitro* studies suggest that the active agents in DEPs that affect IgE production are polycyclic aromatic hydrocarbons (66). Animal studies also demonstrate that polycyclic aromatic hydrocarbons enhance IgE production in animals via actions on B lymphocytes (67). Taken together, these data suggest that diesel particles and DEPs may play a significant role not only in asthma exacerbation but also in T_H2 inflammation via the actions of polycyclic aromatic hydrocarbons on B lymphocytes.

Endotoxin and Asthma

Endotoxin is a common component of PM and is also encountered in domestic (68,69) and occupational settings (70,71). A number of studies have demonstrated increased airway symptoms in workers who encounter high levels of endotoxin in the workplace (70,72–77). Endotoxin is known to stimulate

innate immune responses that have a T_H1 -type character (neutrophilic inflammation, lack of IL-4 and IL-13). Endotoxin induces neutrophilic airway inflammation in nonallergic, nonasthmatic volunteers (78–85). This agent also has been found to enhance nonspecific airway reactivity in asthmatic individuals (86–88).

Recent studies suggest that endotoxin may be a factor in increasing asthma morbidity and wheeze (89,90). Conversely, exposure to endotoxin at a very young age may protect against development of allergic responses to allergens (68). However, in persons with ongoing allergic inflammation, the degree of allergic inflammation, as determined by enumeration of airway eosinophils, appears to correlate with increased response to endotoxin (91). Allergen challenge enhances expression of CD14, an important endotoxin receptor, in asthmatic individuals (92–94) and enhances nasal inflammatory responses to endotoxin, including increases in neutrophils and eosinophils (95). Treatment of asthmatic individuals with corticosteroids blunts response to endotoxin and decreases CD14 expression in the airway (96). Taken together, these observations suggest that allergic inflammation modifies the response to endotoxin, enhancing the impact of this agent on asthma symptoms and morbidity.

Potential Common Mechanisms

Each of the pollutants outlined above can induce neutrophilic inflammation. NF- κ B is a key aspect of such activation. Ozone has been shown to activate NF- κ B in epithelial cells (97) and to induce this transcription factor *in vivo* in animal respiratory tissue (98,99). This activation is blunted by treatment with corticosteroids. Metal ions and diesel exhaust also appear to induce NF- κ B (48). Endotoxin is a classic stimulus for NF- κ B activation (100). Signal transduction of endotoxin after it binds to the CD14 cell surface depends on interaction with the toll-like receptor (TLR) 4. An intriguing linkage between TLR 4, a key receptor for endotoxin, and the action of ozone suggests that TLR4 (or other similar membrane-spanning molecules) may mediate the ultimate activation of NF- κ B by ozone as well (101,102). Future studies on the effect of environmental stimuli in exacerbating asthma should examine potential common response elements such as the TLR 4, which may mediate the effect of a number of apparently disparate pollutants.

Summary

This article has outlined some of the examined effects of ozone, PM, and biological agents on asthma exacerbation. The role of air toxics, an important and commonly

encountered air pollutant, in asthma has not been aggressively studied. Its potential importance is demonstrated by studies of PM in which the active agents are biologically active metal ions and organic residues, both of which can be considered air toxics. This class of compounds may have significant effects on asthma, especially modulating immune function, as demonstrated by the role of polycyclic aromatic hydrocarbons from diesel exhaust in IgE production. Examination of the effect of air toxics in asthma as they exist either in gas, vapor, or particulate form warrants further study.

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