Occupational Asthma

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Many toxic compounds found in air emissions may induce bronchoconstriction. In the workplace, workers are exposed to these compounds, often in much higher concentrations. Some of these compounds act as sensitizers. Of these, some compounds induce asthma by producing specific IgE antibodies to the compound or its protein conjugate, while others induce asthma through yet unidentified immunologic mechanisms. Some compounds, when inhaled in high concentrations, act as irritants and produce bronchoconstriction probably by inducing acute airway inflammation. The latter condition is called Reactive Airways Dysfunction Syndrome (RADS) or irritant-induced asthma. Occupational asthma is an excellent model to study the pathogenesis and the natural history of adult onset asthma because the responsible agent can be identified, complete avoidance is possible, and exposure can be measured or estimated. — Environ Health Perspect 103(Suppl 6):249-252 (1999)

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Introduction

Industry is the largest contributor of emission of toxic compounds into the atmosphere in many parts of the world. An initial list of 189 compounds has been identified by the Clean Air Act Amendments as urban air toxics (1). When inhaled in low concentrations, some of these chemicals may induce bronchoconstriction in subjects with asthma; in high concentrations, they may induce asthma de novo by causing acute inflammation in the airways. In addition, a few of these chemicals are known sensitizers in the workplace. Table 1 shows a list of these compounds. In many instances, workplace exposure to these agents is much higher than those in the urban population. The understanding of the mechanisms of how occupational agents induce asthma in the workplace and the determinants are important for our understanding of air toxic compounds and asthma.

Definition of Occupational Asthma

Occupational asthma is defined as asthma due to causes and conditions attributable to a particular working environment and not due to stimuli encountered outside the workplace (2).

Mechanisms of Asthma Induced by Agents in the Workplace

Over 200 compounds have been identified as capable of causing occupational asthma (3). Interested readers can obtain a comprehensive list of the agents in the book Asthma in the Workplace (2). In general, occupational agents can be divided into two categories by whether they induce asthma through immunologic mechanisms or through nonimmunologic mechanisms:

- Agents that induce asthma through immunologic mechanisms, IgE- or non-IgE-dependent. These include all of the high and some low molecular weight agents. For some agents, particularly the low molecular weight compounds, evidence for an immunologic mechanism is still lacking. The characteristic feature is the presence of a latency period (2).
- Agents that induce asthma through nonimmunologic mechanisms. The best example is illustrated by irritant-induced asthma or reactive airways dysfunction syndrome (RADS) (4).

Under certain exposure conditions, immunologic and nonimmunologic mechanisms may coexist.

Agents That Induce Asthma through an IgE-dependent Mechanism

These include high molecular weight (>5000 daltons) compounds such as flour, laboratory animal proteins, detergent enzymes, and a number of low molecular weight (<1000 daltons) compounds such as acid anhydrides and metals. It has been postulated that the low molecular weight compounds combine with body protein to form complete antigens. It is the latter group of compounds that is of special interest to researchers of urban air toxic chemicals and asthma, as some of these agents are listed among the 189 toxic compounds (Table 1) (2).

Specific IgE antibodies have been identified against extracts of these high molecular weight compounds and the hapten-protein conjugates of low molecular weight compounds either by skin tests or by the RAST method (5). These agents are not different from common inhalant allergens. The mechanisms of IgE-mediated allergic reaction in the skin and the airways have been extensively studied and will not be discussed here.

Agents That Induce Asthma by Non-IgE-dependent Mechanisms

These are usually low molecular weight compounds. Among these compounds, the most common one causing occupational asthma is isocyanates. The isocyanates, toluene diisocyanate (TDI) and

Table 1. Known occupational sensitizers listed as air toxic compounds.*

| IgE-Dependent mechanism | Non-IgE-dependent mechanisms |
|-------------------------|-------------------------------|
| Phthalic anhydride      | Toluene diisocyanate          |
| p-Phenylendiamine       | Diphenylmethyle diisocyanate  |
| Non-IgE-dependent        | Hexamethylene diisocyanate    |
| mechanism               | Acetaldehyde                  |
|                         | Formaldehyde                  |
|                         | Nickel compounds              |
|                         | Cobalt compounds              |
|                         | Chromium compounds            |
|                         | Hydrazine                     |
|                         | Styrene                       |

*Modified from Leikauf et al. (1).
Diphenylmethyl disiocyanate (MDI) are also listed as urban air toxics (Table 1) (1). Specific IgE antibodies have been identified in only a very small proportion of patients proven to have the disease by inhalation challenge tests (5). Although a specific immunologic mechanism has not yet been identified for isocyanate-induced asthma, the clinical features suggest an allergic disease, i.e., only a small proportion of exposed subjects develop asthma, there is a latency period between the onset of exposure and the onset of asthma, and exposure to a small amount of the causative agent can induce an attack of asthma.

Another example of non-IgE-dependent asthma is red cedar asthma. The offending agent is plicatic acid, which is uniquely present in Western red cedar (6). There have been many studies on the mechanism of asthma due to isocyanate-induced asthma and red cedar asthma. In both cases, the pathological changes in the airways have been studied in detail in bronchial biopsies (7,8). They are similar to those of nonoccupational asthma characterized by sloughing of the epithelium, thickening of the basement membrane, and cellular infiltration, particularly with eosinophils. In both types of asthma, increased numbers of activated T-lymphocytes were found in the bronchial mucosa, which suggests a cellular immune mechanism (7,8). Recent studies suggest that T-lymphocytes may play a direct role in asthma rather than through induction and suppression of IgE synthesis, as T-lymphocytes may release potent cytokines thereby causing direct inflammation (9, 10). In patients with nickel- or cobalt-induced asthma, stimulation of peripheral blood lymphocytes by the salts of the metals showed proliferation (11,12). In red cedar asthma, peripheral lymphocytes of patients have also been shown to proliferate when stimulated with plicatic acid-human serum albumin conjugate in vitro, adding further evidence that T-lymphocytes may be important in either initiating or perpetuating the inflammatory response in the airways (13).

Nonimmunologic mechanisms may also amplify the immunologic response as well. TDI has been found to act as a beta-adrenergic blocking agent (14). It has also been found to inhibit neutral endopeptidases, enzymes that limit the concentration of neuropeptides and stimulate the release of substance P (15). These activities could trigger neurogenic inflammation and precipitate asthma. Plicatic acid has been found to release histamine directly from peripheral leukocytes of some healthy subjects (16) and activate complement pathways (17). These properties could enhance the inflammatory process in the airways.

**Asthma Induced by Nonimmunologic Mechanisms**

The best example of this type of asthma is RADS or irritant-induced asthma, which was first reported by Brooks and coworkers (4) in industrial settings. They described 10 subjects who developed cough, wheeze, and shortness of breath within a few hours of exposure to high levels of irritant vapors, fumes, or smoke. All subjects tested had evidence of nonspecific airway hyperresponsiveness. None of them had a history of respiratory disease in the past. Most of the subjects had persistent asthma and airway hyperresponsiveness several years after the incident. Although the syndrome is called RADS, the clinical picture is that of asthma and should be called irritant-induced asthma (2).

There are now many case reports of RADS after exposure to irritants (14–30). Some of these cases fulfilled all the diagnostic criteria for RADS, whereas others reported that workers developed asthma after several heavy exposures to irritants rather than to one single massive exposure as described in RADS (27, 28). Irritant-induced asthma has been described in pulp-mill workers who had been gassed on several occasions (28). These workers had evidence of either reversible airflow obstruction or evidence of airway hyperresponsiveness.

Bronchial biopsy done on these workers showed changes similar to patients with nonoccupational asthma—sloughing of the epithelium, thickening of the basement membrane, and infiltration of the mucosa by eosinophils (30,31). In one study, immunostaining of the bronchial biopsy showed that, while there were a large number of activated eosinophils, there was a paucity of activated T-lymphocytes supporting the absence of a cellular immune mechanism in these patients (31). In another study, in addition to the above changes, there was an increase in fibrosis of the bronchial wall compared to that in patients with nonoccupational asthma (30).

The pathogenesis of RADS is entirely speculative. High-level irritant exposure probably initiates massive airway injury, leading to massive epithelial damage and destruction. This will lead to the activation of nonadrenergic, noncholinergic (NANC) pathways via axon reflexes and onset of neurogenic inflammation. Nonspecific macrophage activation and mast cell degranulation may also occur with release of proinflammatory chemotactic and toxic mediators. Secondary recruitment of inflammatory cells will then enhance the subsequent inflammatory process (31).

**Determinants of Occupational Asthma**

The development of occupational asthma is dependent on exposure factors, predisposing host factors, and cofactors.

**Exposure Factors**

There are now studies showing that the higher the exposure, the higher the prevalence of occupational asthma (32–34). However, at present there is little information on what is the safe exposure level below which no cases of asthma will occur for any of the occupational agents. It is likely that this level is lower than the threshold limit values set for many compounds. In addition, once a subject is sensitized to an occupational agent, he or she is likely to develop bronchoconstriction at a much lower concentration than the level that led to sensitization. Intermittent high exposure may be more important in inducing asthma; many new cases of TDI asthma occurred after exposure to a spill of the chemical (35). A great deal of research related to exposure assessment is needed.

**Predisposing Host Factors**

Predisposing host factors are different for IgE-dependent and non-IgE-dependent causes. Atopy and smoking are important host determinants for agents that induce asthma through an IgE-dependent mechanism. The majority of patients with IgE-dependent occupational asthma are atopic subjects (5). Smoking has been found to be an important determinant for sensitization. A prospective study of platinum refinery workers has shown that about 70 to 80% of smokers were sensitized to platinum salt after a period of 4 to 5 years as opposed to less than half of the nonsmokers (36). A study of workers exposed to tetrachlorophthalate anhydride has demonstrated that atopic smokers had higher prevalences of sensitization than atopic subjects alone, indicating that there is interaction between atopy and smoking (37). This is a very interesting observation, as it parallels the observation that exposure to environmental tobacco smoke, containing many air toxic compounds, not only is an important factor in aggravating the
severity of asthma in children (38) but also may be responsible for increasing the incidence of asthma in high-risk infants (39).

Both atopy and smoking are not important predisposing host factors for agents that induce asthma through non-IgE-dependent mechanisms. In TDI-induced asthma and red cedar asthma, the majority of patients are nonatopic subjects and are nonsmokers (5). Thus far, no predisposing host factors have been identified for these types of occupational asthma.

**Outcomes of Occupational Asthma**

Many follow-up studies of patients with occupational asthma due to various agents have shown that the majority failed to recover even after years of removal from exposure (5). Since these patients did not have asthma before employment and they had a specific reaction to the offending agent, one can only assume that the persistence of symptoms is due to previous occupational exposure. This finding suggests that once an individual develops asthma from any stimulus, self-perpetuating processes may be responsible for the chronic inflammation in the Airways resulting in persistence of nonspecific bronchial hyperresponsiveness and asthma symptoms.

**Definition and Pathogenesis of Occupational Asthma**

There are various studies of the natural history of asthma from the premorbid state to the development of disease and of the interaction between predisposing host factors and the environment. It has been difficult to carry out such a study for many reasons: a) early age of the onset of the disease, b) sensitivity to multiple allergens rather than to one, c) difficulty in estimating the dose and duration of exposure to the allergens, and d) difficulty in achieving complete environmental control.

On the other hand, occupational asthma occurs in adulthood and is caused by one agent most of the time. The dose and duration of exposure can be measured or estimated. Complete environmental control can be achieved by removing the individual from exposure. Occupational asthma is the only reasonable model for studying the natural history of asthma; one can examine workers before employment in a high risk industry and follow them regularly for the development of sensitization or asthma. It has the added advantage that the asthmatic symptoms can be reproduced in a laboratory in a controlled manner. It is therefore also an ideal model to study pathogenic mechanisms of disease. Moreover, different occupational agents can cause asthma through different mechanisms. Thus, these agents can provide models for studying asthma induced by air toxic compounds that are also likely to cause asthma through different mechanisms.

A great deal has been learned about the pathogenesis, development, progression and outcome of asthma from occupational exposure. The methods used in these studies and the knowledge attained can be used in studies of air toxics and asthma.

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