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REVIEW PAPERS

NON SPECIFIC ENVIRONMENTAL FACTORS AND ASTHMA DEVELOPMENT

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Abstract. Environmental pollutants seem to be responsible for dramatical increase of allergic disorders that have been observed lately. The best documented environmental factors facilitating allergy development are: ozone, diesel-exhaust particulate matter and tobacco smoke. Formaldehyde and SO_2 seem to be also very important but still are not sufficiently documented. Mechanisms involved in allergy promotion include: better penetration of allergens across respiratory mucosa or direct modulation of immunological response.

INTRODUCTION

Trends of increasing asthma prevalence and asthma mortality have been reported since 1970 (74). In the United States during a 6 year period from 1979 to 1984 death caused by asthma increased by 37% (69). The most dramatic increase has been observed in childhood asthma incidence (21). Unfortunately, it has been suggested that the severity of asthma is also increasing (4).

Some evidence suggests that the regular treatment with beta-2-agonists may be harmful (65, 75). Another possible explanation may be environmental pollutants. In many countries the levels of exposure in the ambient environment have improved lately; however there are places that exceed the current standards for certain pollutants on a regular basis. In these places a significant increase of asthma prevalence was noted (80).

Chronic respiratory diseases occur up to 4 times as often in men as in women. This difference is explained mostly by differences in the smoking rate and partly by occupational exposure (17). However, in the developing countries of Central and South America the ratio is much closer and often below 1.0. Certainly, there is no evidence in these regions that women smoke more than men: it is reasonable to attribute the relative excess in women to alternative forms of exposure such as environmental factors (80).

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OZONE

Epidemiological studies indicate that community exposure to low concentrations of ozone can affect human health (51,78) Ozone is the major component of photochemical smog. Acute exposure changes in respiratory function, produces airway inflammation with a massive neutrophil infiltration and increases the level of bronchial hyperresponsiveness (9, 27, 30, 31, 35, 42, 51, 76). Animal studies have provided a more direct evaluation of ozone toxicity. It has been shown that short-term exposure to less than 1.00 ppm induces injury of bronchial epithelium and alters the permeability properties of mucosa (11, 12, 15, 25). The latter mechanism may lead to better penetration of inhaled allergens across the bronchial wall to a tissue rich in immunological competent cells and target cells of allergic reaction. As for higher O_3 concentrations exposed to guinea pigs, mice and dogs have been shown to increase allergens responsiveness of the airways by a mechanism involving an increased access of allergen to subepithelial mediator secreting cells (62, 63). Other investigations dealing with animal models have indicated that O_3 exposure may also increase IgE – dependent sensitization of the lower respiratory tract (23).

Children exposed to ambient concentrations of O_3 during normal outdoor activities experience a persistent decrease in peak expiratory flow rates (44, 78). It has been shown that hospital admissions were associated with increased concentrations of O_3 (1). Short term exposure to ozone (120 – 140 ppb for 2 – 4 h) during moderate exercise produces a significant fall of spirometric parameters (79). Although the majority of human studies focused on the lung or lower airways, it has been recently demonstrated that approximately 40% of inhaled O_3 is removed by the nose producing neutrophils influx and nasal inflammation (39).

SULPHUR DIOXIDE AND SULPHURIC ACID

SO_2 is a common environmental pollutant evoking bronchoconstriction both in animals and in man. SO_2 dilutes in water and may act via hydrogen ions released by sulphorous acid. Aerolised sulphuric acid is a much more potent irritant to man than is sulphur dioxide (64). H_2SO_4 exposure at concentration 100 ug/m^3 for one hour produces alterations in the mucocilliary clearance rate in human adults and alterations in respiratory mechanics in exercising adolescent asthmatics (40, 45). In centers of large cities levels of atmospheric SO_4-ions excess 70 ug/m^3, though usually are approximately 20 ug/m^3 (47). In controlled chamber studies such exposure provoked bronchoconstriction and increased bronchial reactivity both in asthmatics and healthy volunteers (29, 32). Evidence from controlled epidemiologic studies supports the aetiologic role of hydrogen ion exposure in evoking asthmatic symptoms (16, 82, 90). The results from studies with healthy volunteers show that short-term exposure to sulphur dioxide at concentrations not exceeding concentrations observed in the ambient environment do not affect the respiratory tract (29). In asthmatic patients, however, such exposure provokes a significant bronchoconstriction with moderate or severe dyspnoea and wheezing (29, 41, 46, 77).

The mechanism by which the inhalation of SO_2 causes bronchoconstriction is [6]still controversial. In humans it appears to differ from parasympathic reflex mechanism demonstrated in cats since pretreatment with vagal antagonists produces only a partial inhibition of SO_2-induced bronchoconstriction. It has been demonstrated in asthmatic subjects that SO_2-induced bronchoconstriction could be inhibited by disodium cromoglycate (DSCG). Since DSCG is a potent mast cell stabilizing agent, this observation may indicate that mast cell may be involved in SO_2-induced bronchoconstriction (57).

SO_2 and suspended particles were suggested as being responsible for many excess deaths before air quality control was investigated. Accompanied by smoke increased daily death rate occurred and sharp illness rates went up in London (58). Some data suggests that a weight per volume measurement of 715 ug/m^3 of SO_2 over a 24 h period combined with a smoke concentration of 750 ug/m^3 causes greater health damage than either of these two factors separately (85).

NITROGEN DIOXIDE

NO_2 is a major ubiquitous environmental air pollutant. NO_2 is also present in cigarette smoke and certain industrial and indoor combustion discharges. The gas possesses powerful oxidating properties (9,10). It has been postulated that it gives rise to free radicals causing cell injuries, since a potent radicals scavenger ascorbic acid administered orally prevented NO_2-induced bronchial hyperresponsiveness (56). NO_2 due to its low solubility is, to a large extent, deposited in the peripheral spaces where it acts on cells according to its oxidant and free radicals properties (72). Morphological studies in animals have shown that the most sensitive part of the lung to NO_2 exposure is found in the transitional zone between the terminal bronchioli and the alveolar ducts (20). In bronchoalveolar lavage (BAL) fluid in animals an increased number of neutrophils and macrophages, and in some investigations also lymphocytes and mast cells were found (18, 71). NO_2 exposure has also been shown to cause an altered antiprotease activity and impaired macrophage function (18, 19). These observations correspond with epidemiological studies proposing increased susceptibility to viral infections following NO_2 exposure (81).

Some authors suggested that NO_2 in a gas cooker stove is sufficient to evoke respiratory illness but no convincing data was presented. The results of controlled human studies seem to be controversial but the majority of authors have not found significant changes of pulmonary function tests in subjects exposed to NO_2 at concentrations of ambient environment (8, 16).

There are few reports of bronchial hyperreactivity after short-term exposure to ambient NO_2 concentrations. In a classic study Orehek at al. found significant increase of bronchial responsiveness after 1 h exposure to 210 ug/m^3 of NO_2 (61). The significant changes in bronchial responsiveness were seen after exposure to low NO_2 concentrations but not after the highest concentrations. Such a relationship may be explained by competing NO_2-induced effects on the airways (8).

FORMALDEHYDE

Formaldehyde (CHOH) is a comomon environmental pollutant, one of the major indoor and occupational factors of exposure. For many years it has been

considered as a potential cause of bronchial asthma and other allergic disorders. The results of our study did not confirm that CHOH could induce asthma and we do not believe that this substance is capable of being a respiratory sensitizer (24). Ambient CHOH affects however the upper and lower airways as an irritant factor. Significant bronchospastic reactions in occupationally exposed asthmatic or bronchitic patients may occur. The eyes of human subjects react with irritation to as little as 0,012 mg/m^3 and irritant reactions in the nose were also observed (2, 67). Such concentration may be detected in homes and it seems to be possible that indoor CHOH produces also bronchial hyperreactivity and bronchial obstruction in allergic subjects.

Formeldehyde is an upper respiratory tract irritant that is highly soluble in the upper airway mucosa. Cellular changes associated with exposure of the respiratory tract to CHOH include alteration of cilia and hypertrophy of the goblet cells (55). Such changes may facilitate allergen penetration across the mucous membrane. CHOH may also contribute to allergic disorders because it penetrates the immune system deeply potentially changing its properties (86). CHOH binds to "scavenger" receptor on macrophages and endothelial cells. CHOH – treated serum albumin is then rapidly transferred intracellulary to lysosomes and stored without degradation (14). No convincing data on possible proallergic CHOH influences was presented but in the light of the above mechanism such properties of CHOH seems to be possible. Significantly greater prevalence rates of asthma and chronic bronchitis were found in children from houses with CHOH exposure levels 60 – 12 ppm than in those less exposed, especially in children also exposed to environmental tobacco smoke (43).

TOBACCO SMOKE

Many studies have reported increased levels of serum IgE in smokers (6, 22, 95). It seems to be important that in ex-smokers total serum IgE level decreases with the increasing number of years of smoking cessation (6). The distribution of skin reactivity is controversial. Some authors reported higher prevalence of positive skin test reactions in smokers and ex-smokers, others observed opposite results (6, 7, 84, 94). O'Connor at al observed that a higher degree of bronchial responsiveness was present in smokers with positive skin prick tests than in smokers with negative skin tests (60). Studies on occupational allergies delivered very interesting observations. Higher values of specific IgE or higher prevalence of subjects with positive skin tests were reported in exposed smokers when compared to non-exposed smokers (91). These results point out that the smoking habit facilitates sensitization in occupationally exposed workers (87).

Not only active smoking but also passive exposure facilitate asthma development. Many authors reported a positive correlation between passive smoking and the prevalence of atopic sings (37, 93). Martinez at al found also a dose – response relationship between skin reactivity in children and the number of cigarettes smoked by the parents (49). Also an increased level of IgE in the cord blood of children exposed to maternal smoking during pregnancy was found (48). Cigarette smoking causes airway inflammation and increased permeability of bronchial mucosa or alveolar epithelium (33).

Alveolar macrophages of smokers are more reactive and may facilitate increased sensitization (92). Bloom at al. found also an increased production of specific reagins against bacterial antigens in smokers (3). Some studies suggest that an increased reactivity of CD_4^+ cells may be involved (26). One cannot exclude the role of eosinophils because tobacco smoke is associated with increased peripheral blood eosinophilia (34).

DIESEL-EXHAUST PARTICULATE

Diesel-exhaust particulate (DEP) are chain aggregates of very small, spherical particles. More than 95% of DEP are smaller than 1um (50). DEP remain in the atmosphere for a long period of time and are undoubtedly inhaled by a man. DEP deposit in the respiratory tract but some particles are phagocyted by macrophages and infiltrate into the perialveolar region or enter lymphatic nodes (83).

DEP have an adjuvant activity for IgE antibody production in mice after entry via the respiratory tract (83). It has been shown also that there is an increasing prevalence of hay fever assosiated with sensitivity to local pollens in rural environments with heavy atmospheric pollution caused by diesel engines (70). In Japan a dramatic increase in the prevalence of allergic rhinitis due to cedar pollen has been observed which paralleled the increase in the number of diesel powered cars (53). 13,2% of the school chidren in the areas near a motor way suffered from allergic rhinitis compared to 5% in rural areas (52, 53). Pulmonary function was also found to be affected during a working day with occupational exposure to diesel engine exhausts (89).

WOOD SMOKE

Wood smoke is known to contain many toxic compounds of incomplete combustion including carbon monoxide, CHOH, SO_2 and polycyclic aromatic hydrocarbons (38). In small children the exposure to open fire has been associated with recurrent respiratory tract infections (28, 88). In BAL studies Demarest showed a marked increase in both the percentage and total number of neutrophils in the fluid (82). The alveolar macrophages had significantly reduced migration in response to zymosan-activated serum. As carboxyhemoglobin level increases, macrophage adherence to glass decreases. The phagocytic action of these cells is impaired. Wood smoke may facilitate asthma development by irritant properties and better penetration of allergens across mucosa or also by changing immunological responses to viruses and allergens.

LESS DOCUMENTED FACTORS

Mercuric chloride ($HgCl_2$) has been shown to increase IgE production in humans (36). In a study of rats it was demonstrated that total IgE levels increased strikingly after injection of $HgCl_2$ and the IgE–specific response of ovalbumine (OVA) was potentiated by injections of $HgCl_2$ in susceptible rats (66).

Phtalic anhydride (PA) is widely used in the production of plasticizers as well as alkyleted and unsaturated polystyrene resins and as a curing agent for epoxy resins. PA has irritative and sensitizing properties. It has been suggested also that PA nonspecifically contributes to asthma development since it increases the total IgE level even in workers without PA specific allergic reactivity (59).

Salt consumption is geographically associated with asthma mortality within the UK, and sodium excretion is strongly related to bronchial reactivity (5). One can suggest that the increase in salt intake contributes to asthma development (73).

CONCLUDING REMARKS

Air pollution should be regarded as a nonspecific trigger mechanism of specific sensitization. Epidemiological studies indicate a clear relationship between allergic asthma in children and high air pollution levels.

Mechanisms involved in allergy promotion include:

1. Better penetration of allergens across respiratory mucosa due to irritation by ozone, SO_2, NO_2, CHOH and possibly by other pollutants.
2. Facilitation of specific sensitization by nonspecific changes of immunological response.

The best known sign of nonspecific influences of the pollutants is the observation of the increased level of total or/and allergen specific IgE level in the absence of specific reagins against these factors.

Ozone and DEP seem to be the best documented chemicals facilitating specific sensitization both in humans and in animals. Short-term exposure to O_2, NO_2 and CHOH also contributes probably to specific airways sensitization (68). CHOH is very often considered as an indoor and outdoor factor influencing atopy developmnt (54). It is introduced into the indoor environment by urea formaldehyde resin, tobacco smoke and combustion gases. Among typical indoor pollutants tobacco smoke is the most important factor contributing to specific sensitization. Tobacco smoke is the most important agent even if passively inhaled. Active smokers are known to have higher prevalence rates of positive skin prick tests to inhaled allergens and a higher IgE level. Passively smoking children have also been found to have higher IgE serum levels as compared to controls from nonsmoking families. In animal studies a nonspecific trigger mechanism of tobaco smoke was presented in rats and guinea pigs.

Mucosal inflammation seems to be the most evident mechanism of nonspecific chemical influences. Since OVA given with DEP intraperitoneally also induces high IgE level to OVA it may be concluded that another mechanism may account for the nonspecific sensitization that directly influences the immunological network.

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