Factors governing susceptibility to chemical allergy

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Abstract

Chemical allergy describes adverse health effects that result from the stimulation of specific immune responses by chemicals. Hypersensitivity reactions are the result of normally beneficial immune responses acting inappropriately against benign antigens, causing inflammatory reactions and tissue damage. The two most frequent manifestations of chemical-induced allergy are contact hypersensitivity and respiratory sensitization, both of which can have serious impact on quality of life, and represent a common occupational health problems. Chemical agents cause approximately 30% of cases of occupational asthma and roughly 90% of these cases involve immunological mechanisms (allergy). Over the past few decades industrialized countries have witnessed a significant increase (although the rate of increase has recently slowed) in the prevalence of atopic diseases including atopic rhinitis, bronchial asthma and urticaria.

Many factors, both intrinsic and extrinsic, can contribute to the development of chemical allergy. In particular, the immune response can be affected by the genetic background, pathological conditions, hormonal and central nervous system status, etc. and by chemical related factors, e.g. dose level, frequency, route and duration of exposure, biotransformation, pharmacokinetics, chemical reactivity, etc. Furthermore, chemical pollution, indoor environment, diet, vaccination programs and the “hygiene hypothesis” have also been implicated in the increased prevalence of asthma and atopic diseases. Following the influence of condition of exposure, heritable and acquired factors, such as age, genetic background, gender etc. on chemical allergy is discussed.

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1. Introduction

The immune system is a sensitive target for many classes of xenobiotics including drugs. This is due as much to the general properties of the chemical (e.g., reactivity to macromolecules), as to the complex nature of the immune system, which encompasses antigen recognition and processing, cell activation, cooperation, regulation, proliferation and differentiation, and mediator production.

The prevalence of asthma and atopic allergy has increased dramatically over the last three decades in westernized countries as a result, probably a combination, of “ill-defined” changes in living conditions in modern societies. A contribution of changes in our genetic background is unlikely since it would take more than several generations to occur, but genetic predisposition is clearly important with regard to susceptibility to allergy. It is believed that exposure to air pollutants, including ozone, diesel exhaust particles, tobacco smoke, may all contribute to this trend. In addition, indoor exposures to allergens and other factors, including dampness and moulds, have been implicated in the increased incidence of asthma. Other individual factors, such as obesity, change in diet, decreased exercise and
increased viral respiratory infections, are all possible contributors (Selgrade et al., 2006).

Chemicals, as well as proteins, are able to induce allergic reactions. Most chemical allergens are less than 1000 Da and are electrophilic or hydrophobic, as such they act as haptons and have to form a stable link with carrier proteins to form a complete allergen. Some of them are not inherently allergenic and must undergo metabolic transformation before participating in an allergic response.

Allergic disease develops normally in two temporally discrete stages: the induction or sensitization phase and the elicitation phase. Hypersensitivity is not manifested on first contact with the antigen (induction phase), but usually appears on subsequent encounter (elicitation phase). Cross reactions between chemicals may occur if they share functional groups critical to the formation of complete allergens.

Allergic contact dermatitis is a form of delayed-type hypersensitivity reaction and as such is dependent upon cell-mediated immune function and the activity of T lymphocytes. It is characterized in sensitized subjects by an eczematous reaction at the point of contact with the allergen. The manifestation of allergic contact dermatitis is dependent upon the primary sensitization of an individual to a specific chemical following dermal exposure. Sensitization usually takes 10–14 days in humans. Exposure to the same antigen will result in elicitation of the inflammatory reaction after a characteristic delay of usually 12–48 h (the elicitation phase). Allergic contact dermatitis is a multifactorial disease, the onset of which is dependent upon on the nature of the chemical, concentration, type of exposure, age, sex, and genetic susceptibility. Cutaneous allergens are generally low molecular weight (hapten). It is clear that some allergens (e.g., urushiol, dinitrochlorobenzene, oxazolone, diphenylcyclopropenone) are very potent sensitizers and appear able to induce sensitization virtually in all normal people, whereas others (e.g., metallic salts of nickel, cobalt and chromium, and a variety of organic compounds) are somewhat weaker allergens and appear only to sensitize susceptible individuals (Kimber and Dearman, 2002a).

Some chemical allergens (fewer in number than contact allergens) have the ability to cause allergic sensitization of the respiratory tract. Chemical respiratory allergy, although less common than allergic contact dermatitis, is of considerable significance, not least because asthma resulting from sensitization can be severe, or even fatal. A variety of chemicals has been implicated as causing occupational respiratory allergy. Among these are diisocyanates (such as toluene diisocyanate and diphenylmethane diisocyanate), acid anhydrides (including trimellitic anhydride and phthalic anhydride), some reactive dyes, certain chlorinated platinum salts, glutaraldehyde, chloramine-T, plicatic acid and carmine. There is usually a delay of some time between first exposure and the development of symptoms. Once sensitization has been acquired low level inhalation exposure can precipitate early, late or dual-phase reactions associated with frank inflammatory changes. Many acute allergic reactions are effected by IgE antibody. In such instances sensitization is characterized by stimulation of a specific IgE antibody response. Such antibodies distribute systemically and associate with mast cells via specialised membrane receptors. Following subsequent exposure allergen will bind to, and cross-link, membrane-associated IgE antibody. This in turn results in mast cell activation and degranulation, and the release of both preformed and newly synthesised mediators. These latter act in concert to provoke inflammation and the symptoms of an allergic reaction.

Although there is no doubt that specific IgE antibody plays a pivotal pathogenetic role in respiratory allergy to inhaled proteins, there is less certainty with respect to chemical respiratory allergy. This is due largely to the fact that in some investigations, notably of diisocyanate-induced respiratory hypersensitivity, it has been found that symptomatic individuals may lack detectable IgE antibody. In fact, with respect to diisocyanate occupational allergy it has been estimated that in less than half of clinically confirmed cases can specific IgE antibody be found. The corollary is, of course, that in other instances IgE antibody is detectable in diisocyanate allergy. Moreover, in respiratory allergy caused by other chemicals, such as the acid anhydrides, the association between IgE antibody and symptoms is much stronger. Where IgE is present it is highly predictive of occupational disease (Kimber and Dearman, 2002b; Lui and Wisnewski, 2003).

2. Heritable and acquired factors influencing susceptibility to allergy

A variety of “susceptibility factors” need to be considered when evaluating the potential of a xenobiotic to influence adversely the immune system. In Fig. 1 some of the factors influencing the susceptibility to some forms of allergy are shown.

The conditions of exposure (dose, frequency, route, duration) should be considered as well as biophysical properties of the chemical (e.g., toxicokinetics, half life, binding properties) since this can dictate the lymphoid organs that will be targeted, the kind of immune response
elicited and, in some cases, the development of tolerance.

Overall, the bases for inter-individual differences in susceptibility to chemical hypersensitivity are not fully understood, although atopy appears not to be a predisposing factor (Selgrade et al., 2006). In some circumstances, there may be an association to susceptibility with diesel exhaust particles, dampness and moulds, cigarette smoking, and there are interesting suggestions that certain alleles (for instance, major histocompatibility complex genes and glutathione S-transferases) may represent risk factors for chemical-induced hypersensitivity reactions (Mapp et al., 2000, 2002). Severe respiratory viral infections during early age have been associated with a higher prevalence of asthma in later childhood. In established asthma, viral infections are a frequent cause of asthma exacerbation (Van Rijt et al., 2005). Furthermore, the importance of epidermal barrier dysfunction, predisposing to the harmful effects of environmental agents, has also been suggested. Skin barrier function can be impaired by a genetic predisposition to produce increased levels of stratum corneum chymotryptic enzyme. This protease enzyme causes premature breakdown of corneodesmosomes, leading to impairment of the epidermal barrier. This may be relevant for allergic contact dermatitis. The addition of environmental interactions, such as washing with soap and detergents, or long-term application of topical corticosteroids can further alter epidermal barrier function, thereby increasing the risk of allergen penetration and succeeding inflammatory reaction, thus contributing to exacerbations of this disease (Cork et al., 2006). Similarly, there is evidence that better lung functions in childhood is associated with better prognosis in adulthood (Vonk and Boezen, 2006).

Studies of family history and genetic studies of asthma have convincingly shown that allergy has a strong
genetic component, more than 60 reports of genetic variants associated with asthma have been identified (Ober and Hoffjan, 2006; Hoffjan et al., 2003), even if only 8–10 such genes have been confirmed in three or more studies. The immune and detoxification systems are characterized by allelic polymorphisms, which underlie individual differences in ability to deal with pathogens and toxic compounds. The influence of genetic background on the response of the immune system to toxic insult can be seen at different levels: it can influence the metabolism and fate of the xenobiotic, and it can influence the resistance or susceptibility to pathogens or to immune mediated diseases, including allergy. It is likely that the risk of developing asthma is greatest when both genetic and environmental risk factors are present simultaneously.

Cytochrome P450 (CYP) enzymes catalyze the generation of reactive species capable of binding with cellular macromolecules, leading to acute and delayed toxicity. Since individual CYP forms differ markedly in their substrate preferences and regulation, the expression profiles of CYP in various cell types are important determinants in tissue-specific toxicity. Genetic background determines the presence or absence of a specific enzyme, playing a major role in the outcome of toxicity tests (Pelkonen and Raunio, 1997). Approximately 40% of human CYP-dependent xenobiotic metabolism is carried out by polymorphic enzymes, which can cause abolished, quantitatively or qualitatively altered or enhanced xenobiotic metabolism, which is often difficult to predict. The extensive inter-individual variation in human xenobiotic metabolism is a serious challenge in risk assessment. The main causes for the variation in xenobiotics metabolism are once again genetic polymorphism of the CYP, but also the induction or inhibition of CYP due to concomitant drug therapies or environmental factors.

The ability to mount an immune response to any antigen is also genetically controlled. Major histocompatibility class (MHC)-linked genes have been shown to play a part in the immune response to infections as well as to self-antigens and allergens. In some cases the gene involved is in the MHC gene itself, but in others it is believed to be a gene that is linked to the MHC. In general, genes outside the MHC region are considered less polymorphic than MHC genes and they make a lesser contribution to variations in disease susceptibility in a population than do the MHC genes. All autoimmune disorders are associated with the elaboration of autoantibodies and/or the production of self-reactive cell populations. Several autoimmune diseases share similar genetic backgrounds, as reflected by study of loci within the MHC. In part the coassociation is due to common genetic tendencies with different environmental precipitating agents (trigger mechanisms).

The development of polarized Th1 or Th2 responses depends on the individual genetic background and on environmental factors, including dose of antigen, nature of immunogen and on cytokines (IL-12, IFN-γ or IL-4) produced at the time of antigen presentation. Polarized Th1-type and Th2-type responses play different roles in protection and immunopathological reactions, Th1 being effective in the defense against intracellular pathogens and Th2 against parasites. Regarding immunopathological conditions, Th1 responses predominate in organ-specific autoimmune diseases, acute allograft rejection, unexplained recurrent abortions, contact dermatitis and in some chronic inflammatory disorders, Th2 responses predominate in transplantation tolerance, chronic graft versus host disease, systemic sclerosis and in atopic disorders (Del Prete, 1998). From a toxicological perspective modulation of Th cell responses is one means by which xenobiotics may cause immunotoxicity/chemical allergy. A shift from Th1 to Th2 responses can enhance both infections and allergic diseases (Selgrade et al., 1997). Furthermore, genetic predisposition and environmental factors can also affect regulatory T cells (Treg). The Treg-cell response is characterized by an abolished allergen-specific T-cell proliferation and the suppressed secretion of T-helper 1- and T-helper 2-type cytokines. A decrease in Treg functions (i.e. decreased production of IL-10 and transforming growth factor-β, decreased cytotoxic T lymphocyte antigen-4, programmed death-1, and histamine receptor 2 expression) can directly and indirectly increase the risk of allergic and autoimmune diseases (Verhagen et al., 2006).

The immune response is not only dependent upon host genetic predisposition, but it is influenced also by age and gender. For the development of allergy it is crucial the age when exposure to the allergen occurs: fetus, infant, childhood, adult or elderly. Immunotoxicological studies have indicated that exposure to chemicals early during development of the immune system (i.e., prenatal and/or neonatal) transiently or permanently impairs immune responses evaluated during adulthood. Even if largely unknown, the capacity of the immune system to discriminate between “dangerous” and “harmless” antigens appears to develop with age and exposure to microbial flora (Bailey and Haverson, 2006). However, although aging is associated with a general decline in immune function, it is still a matter of debate whether incidence of asthma changes in the elderly. Both antibody and cell-mediated immune responses are affected, T-cell responses being more severely compromised than.
B-cell responses (Burns and Goodwin, 1997; Doria et al., 1997), making unlikely the development of hyper-sensitivity to new allergens in the elderly.

There is a large body of evidence that sex hormones, in particular estrogens, are involved in immunoregulation. Males generally produce less antibodies following antigenic stimulation compared with females, and in mice castration negates this effect. In humans serum IgM concentrations are consistently higher in female than males. However, cell-mediated immunity is somewhat depressed in female. It is known that in young adults some allergic diseases are more common in women than in men (Webb and Lieberman, 2006). The pooled estimate of incidence of asthma among general population has been evaluated to be, respectively, 5.9 and 4.4 per 1000 person-years in women and men, respectively (Eagan et al., 2005). The effects of sex hormones (androgens suppressing and estrogens accelerating) the disease process, appears to result from alterations in T cell regulation.

3. Conclusion

A variety of factors complicate the assessment of immune competence. In particular, the immune response can be affected by host-related factors, e.g. genetic background, age, gender, nutritional, hormonal, and central nervous system status and pathological conditions, and by chemical related factors, e.g. dose level, frequency and duration of exposure, chemical reactivity, biotransformation and toxicokinetic. The induction of allergy is the result of complex interactions between specific exposures and genes that interact with such exposures during crucial period of life. All these factors and interactions need to be considered in providing a holistic view necessary to identify the real risks associated with the exposure to a xenobiotic and to generate public health interventions aimed at reversing the existing trend.

References