Toxicology 318 (2014) 32–39

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Review

Chemical respiratory allergy: Reverse engineering an adverse outcome pathway

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ARTICLE INFO

Article history:
Received 6 January 2014
Received in revised form 30 January 2014
Accepted 4 February 2014
Available online 15 February 2014

Keywords:
Sensitisation of the respiratory tract
Respiratory allergy
Occupational asthma
Adverse outcome pathway

ABSTRACT

Allergic sensitisation of the respiratory tract by chemicals is associated with rhinitis and asthma and remains an important occupational health issue. Although less than 80 chemicals have been confirmed as respiratory allergens the adverse health effects can be serious, and in rare instances can be fatal, and there are, in addition, related socioeconomic issues. The challenges that chemical respiratory allergy pose for toxicologists are substantial. No validated methods are available for hazard identification and characterisation, and this is due in large part to the fact that there remains considerable uncertainty and debate about the mechanisms through which sensitisation of the respiratory tract is acquired. Despite that uncertainty, there is a need to establish some common understanding of the key events and processes that are involved in respiratory sensitisation to chemicals and that might in turn provide the foundations for novel approaches to safety assessment. In recent years the concept of adverse outcome pathways (AOP) has gained some considerable interest among the toxicology community as a basis for outlining the key steps leading to an adverse health outcome, while also providing a framework for focusing future research, and for developing alternative paradigms for hazard characterisation.

Here we explore application of the same general principles to an examination of the induction by chemicals of respiratory sensitisation. In this instance, however, we have chosen to adopt a reverse engineering approach and to model a possible AOP for chemical respiratory allergy working backwards from the elicitation of adverse health effects to the cellular and molecular mechanisms that are implicated in the acquisition of sensitisation.

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1. Introduction

Chemical respiratory allergy is an important occupational health problem, with serious clinical consequences (Ross and McDonald, 1996; Mapp et al., 2005; Diar Bakerly et al., 2008). Less than 80 chemicals have been shown to cause respiratory allergy in humans

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http://dx.doi.org/10.1016/j.tox.2014.02.001
0300-483X/

linked with occupational asthma and rhinitis. Lists are available elsewhere, but among the classes most commonly implicated are the diisocyanates, acid anhydrides, chloroplatinate salts and reactive dyes (Kimber and Dearman, 1997; Baur, 2013).

The challenges for toxicologists in identifying and characterising hazards and assessing health risks for respiratory allergy caused by chemicals are substantial. The situation is very different to that of skin sensitisation for which validated methods for toxicological evaluation are available, together with well established paradigms for risk assessment. No validated methods exist for chemical respiratory allergy. The approaches that have been proposed, or are being explored currently, may have some utility but are far from validation and adoption (Holsapple et al., 2006; Kimber et al., 2007; Boverhof et al., 2008; Isola et al., 2008; Basketter and Kimber, 2011).

The difficulty in developing widely accepted methods for assessment of chemical respiratory allergy have been compounded by two issues.

The first of these is the considerable uncertainty that exists regarding the mechanisms through which chemicals are able to induce allergic sensitisation of the respiratory tract. Respiratory allergy to proteins is associated with, and driven by, specific IgE antibody, and on that basis it would appear reasonable to suppose that the same or a similar mechanism might be relevant for respiratory sensitisation to chemicals. However, although IgE antibody has been associated with many, if not all, chemicals that are known to cause allergic sensitisation of the respiratory tract, the correlation with symptoms is not always strong. In the case of acid anhydrides there has often been found a close association between symptoms and IgE antibody. An example is provided by tetrachlorophthalic anhydride (TCPA) (Howe et al., 1983). However, with some other allergens, and in particular in the case of diisocyanates, only a fraction of symptomatic patients have detectable levels of serum IgE antibody (Cartier et al., 1989; Vandenplas et al., 1993; Cullinan, 1998; Kimber et al., 1998, 2011; Tee et al., 1998; Tarlo, 1999; Kimber and Dearman, 2002a). For instance, it was reported in one study that less than 30% of patients with occupational asthma, and with a positive provocation test, displayed detectable IgE antibody levels (Tee et al., 1998). It can be argued that, for various reasons, the level of association between symptoms of occupational asthma and IgE antibody is much closer than is presently appreciated. For instance, there are significant technical challenges in measuring IgE antibodies specific for a chemical allergen, not least because there is a need to engineer appropriate hapten–protein conjugates for use as substrates in analytical systems (Kimber and Dearman, 2002a). For other reasons as well a case can be made for IgE antibody having a more important role in the acquisition of respiratory sensitisation to chemicals than is generally accepted. However, even if that is the case, the fact remains that an inability to confirm an association with IgE antibody means that there is still doubt as to whether IgE plays a mandatory or universal role in respiratory allergy and occupational asthma (Kimber and Dearman, 2002a, 2005). The inference is, of course, that there may therefore exist immunological mechanisms, other than those that rely on the elaboration of specific IgE antibody, that are able to cause the effective acquisition of respiratory sensitisation. However, there is no consensus on what those other mechanisms are, although by definition the acquisition of allergic sensitisation requires the elicitation of an adaptive immune response of some sort. This is a point that will be returned to later and discussed in greater detail.

The second issue that has contributed to the difficulty of developing methods for assessment of chemical respiratory allergens involves consideration of relevant routes of exposure. It has commonly been assumed that sensitisation of the respiratory tract to chemicals will be acquired solely by inhalation exposure. However, there is reason to be believe, from studies in experimental animals and from clinical experience, that effective sensitisation of the respiratory tract can also be achieved via skin exposure to the relevant chemical allergen (Karol et al., 1988; Botham et al., 1989; Rattray et al., 1994; Kimber and Dearman, 2002a; Tarlo and Malo, 2006; Bello et al., 2007; Redich and Herrick, 2008; Redlich, 2010). This makes sound immunological sense; there is no reason why the skin should not support the quality of immune response required to result in sensitisation of the respiratory tract. In this context it is important to appreciate that the skin is known to be a very effective route for the induction of immune responses to a range of antigens and allergens, and in fact in many instances exposure via the skin may result in more vigorous responses than those from inhalation exposure (Rattray et al., 1994). Acknowledgement that sensitisation of the respiratory tract to chemicals can be achieved via skin exposure has important practical and theoretical implications.

From a practical perspective the ability of skin exposure to support respiratory sensitisation indicates that this is a legitimate route for delivery of test chemicals in assays designed to assess the ability of materials to cause sensitisation of the respiratory tract.

The theoretical implication of the skin being an effective route for sensitisation of the respiratory tract is that whatever mechanisms are involved in the acquisition of sensitisation they must be available both in the skin and in the airways. That is, it is not possible to invoke as potential mechanisms for respiratory sensitisation those that rely on cells, molecules, or tissue microenvironments that are only available in the airways.

Against that background the aim of this article is to describe briefly one potential pathway that may explain the basis for the development of chemical respiratory allergy. This is not an exhaustive or systematic survey of the available literature, but rather an attempt to provide one perspective on the events and processes that may cause sensitisation of the respiratory tract by chemical allergens. For this purpose we have worked backwards from a consideration of the elicitation of adverse reactions in the respiratory tract to the events that cause immunological priming, and from there to speculate how chemical respiratory allergens may be recognised and then processed and presented to the immune system. Working backwards in this way from the adverse health outcome this exercise is, in effect, a reverse engineered adverse outcome pathway (AOP). In 2012 the Organisation for Economic Cooperation and Development (OECD) launched a programme to develop AOPs as analytical constructs that describe series of linked events that are causally related and that lead to an adverse health/environmental effect (Ankley et al., 2010; Vinken, 2013). The general trajectory of an AOP is from a molecular initiating event (MIE), through increasing levels of biological organisation and complexity, to the development of an adverse health effect (outcome) at the tissue and/or organismal level. Using this approach an AOP for skin sensitisation has been developed recently (Organisation for Economic Cooperation and Development (OECD), 2012). Adopting the approach of attempting to define one such pathway, but starting from the adverse outcome, then the first issue that has to be addressed is the nature of the mechanism(s) that cause the symptoms of respiratory allergy and occupational asthma.

2. The elicitation of chemical respiratory allergy/occupational asthma

The task here is to explore how occupational asthma associated with chemical sensitisation might be elicited. There is probably a general consensus that in the sensitised subject respiratory allergic reactions will be provoked following inhalation exposure to a sufficient amount of the inducing chemical allergen in an appropriate form. Where there is considerable uncertainty is regarding the nature of the immunological effector mechanism(s) that trigger such reactions.