

Toluene diisocyanate-induced reverse passive cutaneous anaphylaxis caused by IgG antibody

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Toluene diisocyanate (TDI)-induced asthma is a complex lung disease not easily classified as immunologic in pathogenesis. In one study IgE antibodies were demonstrated in approximately 92% of patients.¹ Other studies reported a much lower incidence of IgE antibodies present in subjects (15% to 19%).² A reactive airways dysfunction syndrome has also been described, for which no immunologic mechanism has been found.³ Elevated levels of IgG antibodies have been correlated with isocyanate-induced asthma.⁴ Classically, IgG antibodies are not associated mechanistically with extrinsic asthma. However, in vitro analysis has shown that IgG antibodies could activate haptenized basophils.⁵ We postulated that IgG antibodies might activate mast cells modified by isocyanate haptenization. Such a phenomenon might have a correlation with certain human cases of TDI-induced asthma. In this study we attempted to determine whether IgG antibodies could generate a reverse passive cross-species cutaneous anaphylactic reaction against TDI.

METHODS

Animals

Healthy adult dogs (*Canis familiaris*) of mixed breed were selected for study. The canine model was chosen because canine mast cell IgE receptors cannot bind the Fc portion of the human IgE antibody.⁶ Experiments were performed with the approval of the Animal Care and Use Committee of Northwestern University and

Abbreviations used

HSA: Human serum albumin
TDI: Toluene diisocyanate

with the use of National Institutes of Health publication no. 86-23 (revised 1985) "Guide for the care and use of laboratory animals" as a guideline.

Antigen

TDI (1219 mg/ml) was obtained from Aldrich Chemical Co. (Milwaukee, Wis.). TDI-human serum albumin (HSA) conjugate was prepared and characterized as previously described.⁴

Serum

Serum samples were obtained from a worker in whom hypersensitivity pneumonitis developed after exposure to diphenylmethane diisocyanate.

Measurement of IgG and IgE by ELISA

Previous in vitro studies have demonstrated cross-reactivity among isocyanates.⁷ The ability of this worker's IgG antibody against diphenylmethane diisocyanate-HSA to cross-react with TDI-HSA was evaluated by ELISA. Sera from nonexposed laboratory workers were used as the negative control. The ELISA method was previously described.⁴

Cutaneous reactivity

Animals were anesthetized with sodium pentobarbital (25 mg/kg body weight) before all studies were performed and received 5 ml of 0.5% Evans blue dye intravenously.⁶ Nonirritating dilutions of TDI and serum that did not elicit cutaneous bluing were determined by intracutaneous injection (0.1 ml per site). The negative control and diluent were sodium chloride 0.9%. The nonirritating dilution of TDI was then injected intracutaneously and allowed to haptenize onto mast cells and their bound IgE. After a 30-minute incubation period, the skin sites were challenged with the nonirritating dilution of serum. The nonirritating dilutions of serum and TDI served as negative controls. A positive reaction

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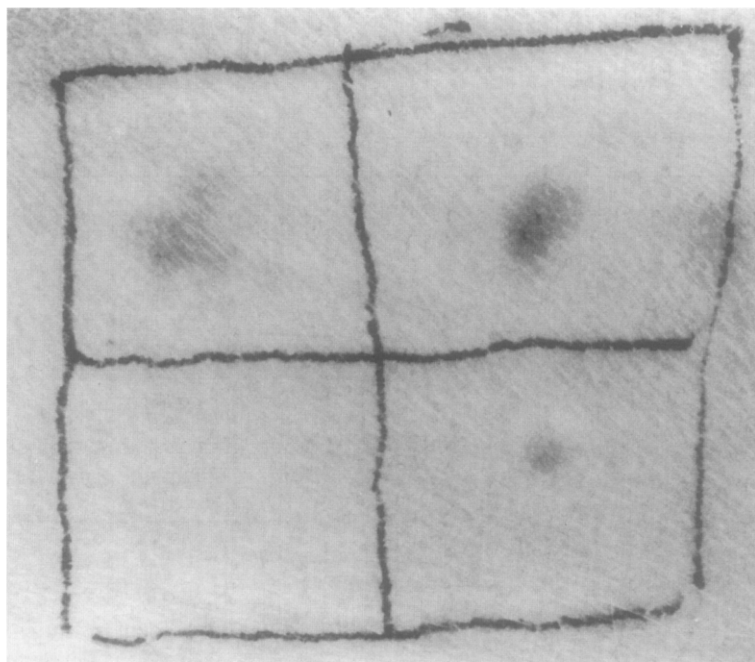


FIG. 1. TDI-induced reverse passive cutaneous anaphylaxis in a canine recipient. **Top row,** TDI (1:10,000) incubated for 30 minutes, showing greater than 10 mm bluing after intracutaneous challenge with serum containing IgG antibody against TDI-HSA (1:512). **Bottom row,** Negative dilution of serum (1:512) alone (*left*) and dilution of TDI (1:10,000) alone (*right*), both showing less than 10 mm of bluing.

was defined as an area that elicited greater than 10 mm of cutaneous bluing within 15 minutes of the challenge.

RESULTS

ELISA

The IgG titer to TDI-HSA was greater than 1:1000. The IgE titer to TDI-HSA was negative.

Cross-species reverse passive transfer

Reverse passive transfer of IgG antibody against TDI was positive within 15 minutes. Serum alone and TDI alone remained negative throughout (Fig. 1). The experiment was repeated on three separate occasions.

DISCUSSION

Isocyanate-induced asthma has a complex immunologic mechanism that is not restricted to a classical IgE antibody-mediated phenomenon. An earlier *in vitro* study of trimellityl anhydride-induced disease suggested that IgG antibody directed against basophil IgE haptenized trimellityl determinants could cause histamine release.⁵

Serum containing a high titer of IgG antibody that was capable of binding TDI-HSA was used in our study. This serum did not contain detectable IgE antibody against TDI-HSA as determined by

ELISA. However, to avoid potential confusion caused by any IgE antibody against TDI-HSA that may not have been detected by ELISA, a canine recipient was chosen for the *in vivo* study. Previous studies have shown that heterologous transfer of serum is limited by phylogenetic differences. Specifically, human IgE antibody cannot functionally interact with canine mast cells to cause histamine release.⁶ The observed cutaneous reaction caused by IgG against TDI-HSA occurred within 15 minutes of challenge, which is consistent with an immediate hypersensitivity reaction.

IgG antibody against TDI-HSA may cross-link TDI bound to mast cell IgE antibody, resulting in histamine release. This model may explain the association of elevated levels of IgG antibody with TDI-induced asthma⁴ by showing that IgG antibody may participate in an immediate hypersensitivity reaction. In addition, it is consistent with evidence that IgE antibody is not a common clinical factor associated with TDI-induced asthma. We do not believe that complement, anaphylatoxins, or any other indirect mechanisms were responsible for the observed phenomenon because the serum control was negative. It appears that some cases of isocyanate-induced asthma may have an IgG antibody-mediated mechanism, as

demonstrated by TDI-induced reverse cross-species passive cutaneous anaphylaxis.

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X-linked agammaglobulinemia presenting as transient hypogammaglobulinemia of infancy

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X-linked agammaglobulinemia (XLA) is an X-linked recessive severe life-threatening disease characterized by the absence of B lymphocytes, total absence or severe deficiency of all immunoglobulin classes, and recurrent bacterial infections with pyogenic pathogens.¹ It has recently been associated with mutations and deletions in a gene encoding for a cytoplasmic tyrosine kinase (Bruton's tyrosine kinase [BTK]).² Typically, XLA can be differentiated from transient hypogammaglobulinemia of infancy (THI); the latter is characterized by low levels of immunoglobulin with intact antibody responses, normal lymph tissue and B-cell numbers, and milder infectious problems. It is often difficult to clinically differentiate XLA from common variable immunodeficiency disease (CVID), a heterogeneous group of disorders char-

Abbreviations used

BTK:	Bruton's tyrosine kinase
CVID:	Common variable immunodeficiency disease
THI:	Transient hypogammaglobulinemia of infancy
XLA:	X-linked agammaglobulinemia

acterized by variable mild, moderate, or severe deficiencies in IgG, IgA, and IgM and recurrent bacterial infections. In CVID, B-cell numbers are characteristically normal. Classification of XLA and CVID is based on major differences in the severity of the depression of immunoglobulin levels. In this report we present a patient with the phenotype of THI who was later thought to have CVID and was eventually found to have XLA on the basis of a mutation in the *BTK* gene. This patient thus represents an example of the extreme variation that can occur in XLA phenotype.

METHODS

Blood was obtained for immunologic and genetic analyses. Immunoglobulin levels were measured by ra-

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