

Mechanisms of drug-induced allergic contact dermatitis

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Abstract

Allergic contact dermatitis is induced by a wide variety of drugs that trigger specific immune responses following topical exposure. Identified chemical structures involved in such reactions include the mercuric and thiosalicylic acid groups of thimerosal, the diphenylketone group of the anti-inflammatory drug ketoprofen, the amide or ester structure of local anesthetics, and the side-chain and thiazolidine ring of β -lactams. The T cell responses to such compounds involve $CD4^+$ and $CD8^+ \alpha\beta^+$ T lymphocytes and also $CD4^-/CD8^- \gamma\delta^+$ T cells. Although “T helper 2” cytokine production by drug-specific human T cells from patients with allergic contact dermatitis has been described, T helper 1-like and T cytotoxic 1-like responses clearly play key roles in this cutaneous reaction.

Abbreviations: ACD, allergic contact dermatitis; DNCB, dinitrochlorobenzene; DNFB, dinitrofluorobenzene; IL, interleukin; IFN- γ , interferon- γ ; MHC, major histocompatibility complex; NSAIDs, nonsteroidal anti-inflammatory drugs; RT-PCR, reverse transcription–polymerase chain reaction; TCR, T cell receptor; Tc1, T cytotoxic 1; Tc2, T cytotoxic 2; Th1, T helper 1; Th2, T helper 2; TNCB, trinitrochlorobenzene, picryl chloride

Introduction

Contact dermatitis can be divided into several categories, based on mechanisms involved in clinical outcomes. Irritant contact dermatitis is essentially an inflammatory response to a direct drug or chemical toxicity on skin cells. Irritant contact dermatitis is local, has a rapid onset, and is mainly characterized by erythema. On the other hand, allergic contact dermatitis (ACD) is a delayed T cell-mediated cutaneous inflammatory response following topical exposure to drugs or chemicals. ACD

is also characterized by possible ectopic cutaneous responses and generalized reactions following systemic administration of the incriminated drug. Histology of allergic contact dermatitis includes perivascular infiltrates of lymphocytes, spongiosis, and edema, leading to possible vesicle formation, parakeratosis, erosions and ulcerations (Nasir and Gaspari, 1996).

Drugs and structures known to be involved in allergic contact dermatitis

Although most immunological mechanisms involved in contact sensitization have been described in experimental models based on study of chemicals, numerous drugs are potential contact sensitizers. The main pharmacological agents involved are topical antibiotics and antiseptics, topical nonsteroidal anti-inflammatory drugs (NSAIDs), dermo-corticoids, estrogens, and topical anesthetics (Guinn and Kincannon, 1997) (Table 1). Professional contact sensitization might also occur with drugs such as propacetamol, sulfonamides, phenothiazines, penicillins and aminoglycosides. The sensitizing moieties of some of these drugs have been studied by assessing cutaneous reactions to structurally related compounds in sensitized patients, or by assessing cross-reactivities of drug-specific human T cell clones. Thus, it was demon-

strated that the sensitizing moieties of thimerosal are both the mercuric moiety and the thiosalicylic acid group and that no sensitized patients react only to the whole molecule of thimerosal (Gonçalo et al., 1996). In addition, the mercuric moiety is involved in cross-reactions with ethylmercuric chloride, while the thiosalicylic acid group is responsible for cross-reactivities with a photoproduct of piroxicam (Cirne de Castro et al., 1991).

Fibric acid derivatives that are frequently used as antilipemic agents can cause photosensitivity and cross-reactivities with ketoprofen have been reported. Based on comparison of chemical structures of both compounds, it can be hypothesized that the diphenylketone group of ketoprofen plays a key role in contact sensitization or photocontact sensitivity (Serrano et al., 1992). This hypothesis is emphasized by the association between contact dermatitis from ketoprofen and the sensitivity to benzophenone-3 (Horn et al., 1998).

Table 1. Principal drugs involved in allergic contact dermatitis

Principal pharmacological categories involved in ACD	Principal active substances involved in ACD
Antibiotics	Aminoglycosides (neomycin ^{a,b} , gentamycin ^c) Sodium fusidate ^d Penicillins ^e
Antiseptics	Halogenated compounds (povidone iodine ^f , chlorhexidine ^g) Ethanol ^h Inorganic mercuric derivatives (mercuric chloride ⁱ) Organic mercuric derivatives (thimerosal ^j , mercurochrome ^k) Quaternary ammonium compounds (cetrimide ^l , benzalkonium chloride ^m)
Contact anaesthetics	Mepivacaine, benzocaine, lidocaine ⁿ , prilocaine ^o
Dermocorticoids	Budesonide (desonide, group B), tixocortol pivalate (hydrocortisone, prednisolone, group A) ^p
Estrogens	17 β -estradiol, estradiol benzoate ^q
Topical NSAIDs	All topical NSAIDs, especially arylacanoic acid derivatives (bufexamac ^r) and anthranilics (ketoprofen ^s)

^aGette and Marks (1992). ^bSherertz (1996). ^cOnder et al. (1994). ^dGiordano et al. (1996). ^ePecegheiro (1990). ^fMochida et al. (1995). ^gKnusen and Avenstorp (1991). ^hOphaswongse and Maibach (1994). ⁱSevila et al. (1994). ^jWantke et al. (1994). ^kGalindo et al. (1997). ^lLee and Wang (1995). ^mCorazza and Virgili (1993). ⁿGall et al. (1996). ^oSuhonen and Kanerva (1997). ^pBurden and Beck (1992). ^qCarmichael and Foulds (1992). ^rCorazza et al. (1993). ^sHorn et al. (1998).

Local anesthetics can be divided in two groups, based on their structure. Amides include lidocaine, mepivacaine, bupivacaine, etidocaine, prilocaine, articaine, and cinchocaine, while esters (the most potential sensitizers among local anesthetics) include procaine, tetracaine, benzocaine, and cocaine. Although it is difficult to identify structures involved in cross-reactivities between the above-mentioned amide-type anesthetics, several reports emphasize cross-reactivities between lidocaine, mepivacaine, bupivacaine, and prilocaine. On the other hand, cross-reactions between amides and esters do not appear to be reported. Thus, the intermediate chain between the lipophilic group and the ionizable group probably plays a key role for the sensitizing potential of local anesthetics (Suhonen and Kanerva, 1997).

The most extensively studied epitopes of drugs involved in hypersensitivity reactions are probably the penicillin epitopes, although β -lactams are mainly responsible for allergic reactions other than contact dermatitis (urticaria, Quincke edema, anaphylactic shock, maculopapular rashes). It is well known that the β -lactam ring of penicillins is the target for nucleophilic attack by lysine residues of protein such as albumin. The structural feature of penicillins recognized by specific antibodies includes the thiazolidine ring, the side-chains, and the protein-bound penicilloyl group. More relevant to contact dermatitis, penicillin-specific T cell clones have been used to determine the penicillin epitopes recognized by $CD4^+$ or $CD8^+$ specific lymphocytes. Experiments by Padovan et al. (1996) clearly show that the epitopes recognized may vary from one T cell clone to another since some T lymphocytes show cross-reactivity with penicillin G, penicillin V, and ampicillin (differing in their side-chain), while other T cell clones react only to penicillin G. On the other hand, none of penicillin-specific T lymphocytes cross-reacts with 6-aminopenicillanic acid

(lacking the side-chain) or with cefaclor (cephalosporin with a dihydrothiazine ring instead of a thiazolidine ring but with a side-chain identical to that of ampicillin). Together, these data from Padovan et al. show that both the side-chain (especially the phenyl group) and the thiazolidine ring play critical roles in activation of T cells.

Principal features of drug-specific T lymphocytes involved in contact dermatitis

Hapten-specific T lymphocytes involved in allergic contact dermatitis can be characterized by their cytokine profile and by the expression of the CD4 or CD8 molecules and $\alpha\beta$ or $\gamma\delta$ T cell receptor.

The delayed-type hypersensitivity to protein antigens is primarily mediated by MHC class II-restricted $CD4^+$ T lymphocytes. By contrast, experimental contact sensitization in the mouse has been utilized to demonstrate that both $CD4^+$ and $CD8^+$ T lymphocytes are activated following topical exposure to sensitizers such as dinitrochlorobenzene (DNCB), trinitrochlorobenzene (TNCB, picryl chloride), dinitrofluorobenzene (DNFB), and formaldehyde (Grabbe and Schwarz, 1998). Human $CD4^+$ and $CD8^+$ drug-specific lymphocytes from patients with contact dermatitis have been isolated and cloned. Zanni et al. (1997) reported that of 57 lidocaine-specific human T cell clones 48 were $CD4^+$, 7 were $CD8^+$, and 2 were $CD4^-/CD8^-$. In addition, it has been extensively reported that β -lactam antibiotics or sulfonamides can trigger human T cell-specific responses involved in immediate-type hypersensitivity reactions or delayed cutaneous reactions such as maculopapular exanthemas, toxic epidermal necrolysis, and acute generalized pustulous exanthema (Hertl et al., 1993; Warrington et al. 1993; Brander et al., 1995; Mauri-Hellweg et al., 1995). However, the involvement and role of $CD4^+$ and $CD8^+$ T

lymphocytes in allergic contact dermatitis remains controversial. Dieli et al. (1997) demonstrated that both MHC class II (I-A)-restricted CD4⁺ and MHC class I (K)-restricted CD8⁺ lymphocytes are activated following topical exposure of mice with picryl chloride and that interleukin (IL)-2 production by CD4⁺ lymphocytes is required for CD8⁺ lymphocyte activation and subsequent elicitation of contact sensitization. Their data illustrate a cooperative function of both cell types for optimal sensitization. By contrast, Xu et al. (1997) reported a CD4⁺ T cell-independent activation of CD8⁺ lymphocytes by oxazolone. Finally, Bour et al. (1995) reported that both MHC class II-deficient mice and normal mice treated with an anti-CD4 monoclonal antibody developed stronger sensitization to DNFB, supporting the idea that CD4⁺ lymphocytes downregulate the inflammatory response during contact sensitization.

The vast majority of peripheral T lymphocytes express a T cell receptor (TCR) composed of two disulfide bond-linked glycosylated polypeptide chains designated α and β . However, a subset of CD3⁺ T lymphocytes bear $\gamma\delta$ TCR. Such lymphocytes have the ability to be restricted by nonclassical MHC-like molecules and have been reported to be augmented in various pathologies including skin disorders (Alaibac et al., 1997). Fujita et al. (1993) reported increased numbers of $\gamma\delta$ TCR-bearing cells in skin lesions 24 h after a DNFB challenge in human volunteers, in the epidermis and in the dermis. Similarly, application of mercuric chloride by a routine epicutaneous patch-testing procedure induces appearance of up to 15% CD3⁺ $\gamma\delta$ ⁺ memory T lymphocytes among dermal CD3⁺ cells in humans (Nordlind and Lidén, 1995). These $\gamma\delta$ ⁺ T lymphocytes do not express the CD4 or CD8 molecule and their precise role remains to be elucidated. Zanni et al. (1997) also reported that CD8⁻/CD4⁻ $\gamma\delta$ ⁺ lidocaine-specific T cell clones can be derived from patients with contact dermatitis, although

the majority of derived clones are CD4⁺ or CD8⁺ $\alpha\beta$ ⁺ T cells.

An important characteristic of T lymphocytes resides in their cytokine secretion profile. Thus, differentiated helper T lymphocytes can be characterized by their pattern of cytokine secretion and be divided into T helper 1 (Th1) and T helper 2 (Th2) subsets. Th1 cells mainly produce IL-2 and interferon- γ (IFN- γ), while Th2 lymphocytes produce IL-4, IL-5, IL-10 and IL-13 (Mosmann et al., 1986; O'Garra, 1998). Similarly, CD8⁺ T cells can be differentiated *in vitro* into T cytotoxic 1 (Tc1) or T cytotoxic 2 (Tc2) lymphocytes (Dutton, 1996). The involvement of Th1- or Th2-like cytokines in contact sensitization has mainly been described in the mouse, with reference compounds such as DNCB, DNFB, TNCB, or oxazolone. All these data clearly demonstrate that strong contact sensitizers activate IFN- γ -producing (Tc1) effector lymphocytes and that IFN- γ plays a central role for the inflammatory cutaneous reaction (Xu et al., 1996). IFN- γ -producing CD8⁺ lymphocytes are activated following chronic exposure of mice to DNCB or formaldehyde, but not to respiratory sensitizers such as trimellitic anhydride (Dearman et al., 1996a,b). In addition, neutralization of IFN- γ at the time of challenge of mice with picryl chloride induces a strong reduction of contact sensitization (Dieli et al., 1997). IFN- γ , however, is not produced only by CD8⁺ T lymphocytes during contact sensitization: depletion of CD4⁺ cells from lymph node cells of formaldehyde-treated mice results in substantial reduction in IFN- γ production (Dearman et al., 1996b). In humans, Zanni et al. (1997) demonstrated that both CD4⁺ and CD8⁺ lidocaine-specific T cell clones produce IFN- γ , although CD8⁺ clones only produce IFN- γ while IFN- γ -producing CD4⁺ cells also produce IL-5 and IL-4. Peripheral blood lymphocytes from patients with contact dermatitis to β -lactams can also be triggered to express IFN- γ mRNA as assessed

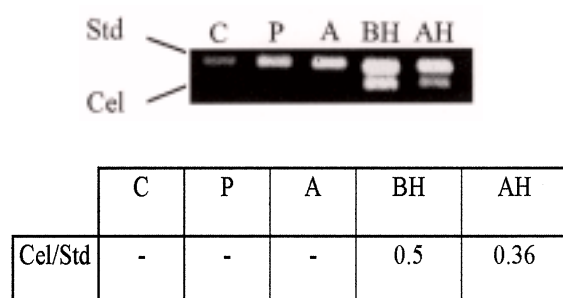


Figure 1. Induction of IFN- γ mRNA in PBMC stimulated with free or conjugated β -lactams. PBMC from a patient suffering from contact dermatitis to penicillin G were stimulated with penicillin G (P), amoxicillin (A), benzylpenicilloyl-serum albumin conjugate (BH), amoxicillin-serum albumin conjugate (AH), or not stimulated (control) (C). The semiquantitative PCR is defined as the competition between a synthetic standard cDNA (Std) and the cellular cDNA (Cel) coamplified with the specific primers. This figure illustrates induction of IFN- γ mRNA following stimulation with BH, and to a lesser extent with AH.

by RT-PCR (Figure 1). Following *in vitro* activation of peripheral blood lymphocytes by free or serum albumin-conjugated β -lactams, total mRNA can be isolated and specific amplification of IFN- γ cDNA can be performed following reverse transcription of mRNA. Coamplification of cellular and standard cDNA allows quantitative or semi-quantitative evaluation of the level of specific mRNA induction. Figure 1 shows preferential induction of IFN- γ mRNA following activation with penicillin and amoxicillin conjugated to human serum albumin, and undetectable induction of IFN- γ mRNA following activation with free drugs. This result strongly suggests the possibility of a CD4⁺-derived production of IFN- γ in this case. Indeed, Brander et al. (1995) previously reported that human penicillin-specific CD4⁺ lymphocytes can be activated by free or conjugated β -lactams, while penicillin-specific CD8⁺ T cells can only be activated by the free drugs.

In conclusion, it should be underlined that many drugs, from various pharmacological categories, are involved in allergic contact dermatitis. Some chemical structures have been identified as involved in such reactions, although unidentified individual factors contribute to this immune-mediated toxic insult. A hapten-specific type 1 (Th1 or Tc1) response seems crucial in elicitation of the cutaneous inflammatory reaction and has been evidenced in experimental murine models and in humans. However, the particular features of the cutaneous drug-specific T cells leading to contact dermatitis (expression of chemokine receptors, adhesion molecules) remain to be precisely determined.

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