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REVIEW

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Anaphylaxis to drugs: Overcoming mast cell unresponsiveness by fake antigens

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Abstract

Our understanding of IgE-mediated drug allergy relies on the hapten concept, which is well established in *inducing adaptive* reactions of the immune system to small molecules like drugs. The role of hapten-carrier adducts in *re-challenge* reactions leading to mast cell degranulation and anaphylaxis is unclear. Based on clinical observations, the speed of adduct formation, skin and in vitro tests to inert drug molecules, a different explanation of IgE-mediated reactions to drugs is proposed: These are (a) A natural role of reduced mast cell (MC) reactivity in developing IgE-mediated reactions to drugs. This MC unresponsiveness is antigen-specific and covers the serum drug concentrations, but allows reactivity to locally higher concentrations. (b) Some non-covalent drug-protein complexes rely on rather affine bindings and have a similar appearance as covalent hapten-protein adducts. Such drug-protein complexes represent so-called "*fake antigens*," as they are unable to induce immunity, but may react with and cross-link preformed drug-specific IgE. As they are formed very rapidly and in high concentrations, they may cause fulminant MC degranulation and anaphylaxis. (c) The generation of covalent hapten-protein adducts requires hours, either because the formation of covalent bonds requires time or because first a metabolic step for forming a reactive metabolite is required. This slow process of stable adduct formation has the advantage that it may give time to desensitize mast cells, even in already sensitized individuals. The consequences of this new interpretation of IgE-mediated reactions to drugs are potentially wide-reaching for IgE-mediated drug allergy but also allergy in general.

KEYWORDS

adducts, anaphylaxis, covalent bonds, drug allergy, fake antigen, hapten, immediate drug reaction, non-covalent bindings, specific IgE

Abbreviations: APC, antigen-presenting cell; BAT, basophil activation test; DC, dendritic cell; DHR, drug hypersensitivity reactions; FAR, fake antigen reactions; FcεRI, high-affinity receptor for IgE; HLA, human leukocyte antigens; HSA, human serum albumin; MC, mast cell; NMBA, neuromuscular blocking agents/muscle relaxants; PPI, Proton-pump inhibitor; RCM, radiocontrast media; SMX, sulfamethoxazole; TCR, T-cell receptor for antigen.

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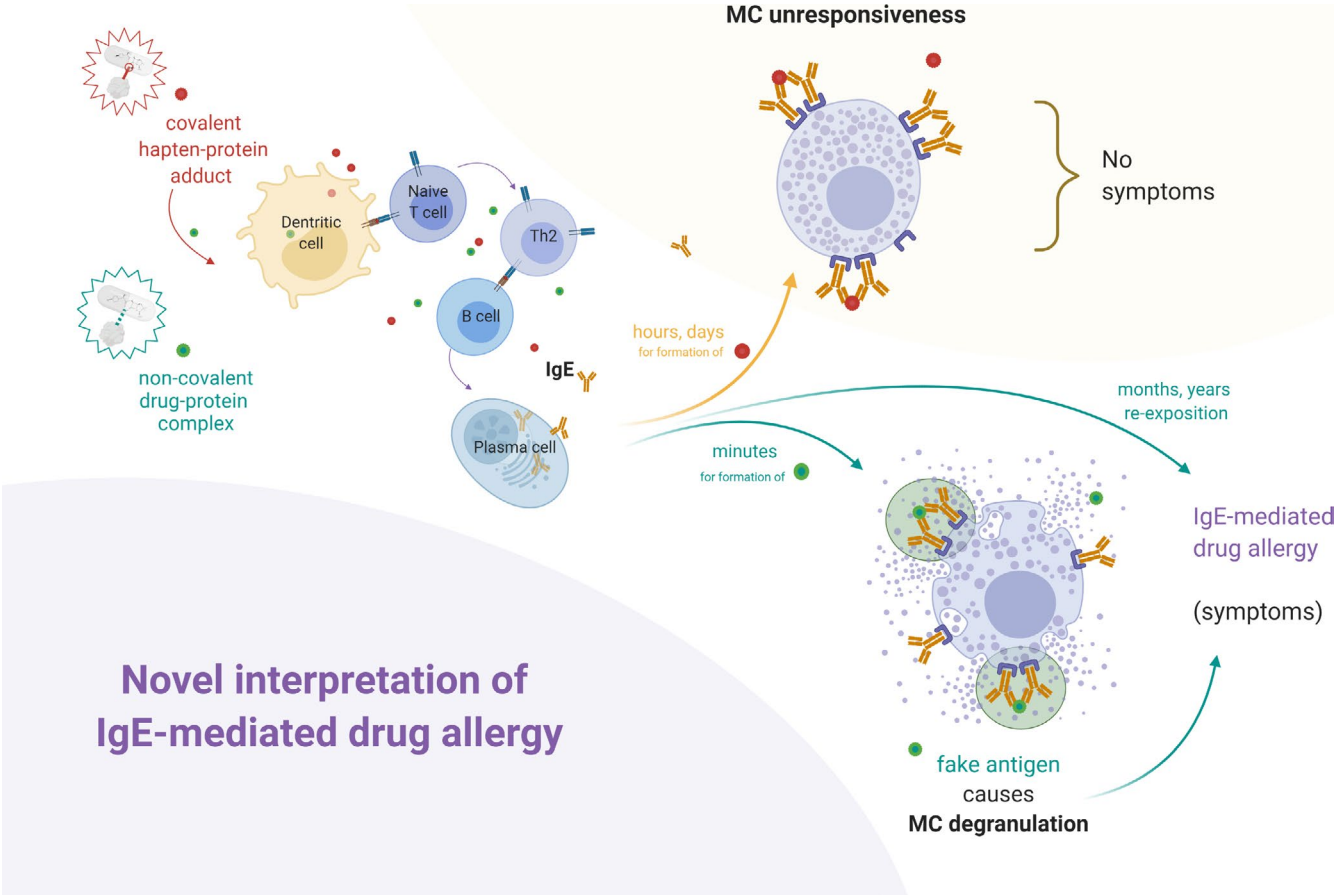

GRAPHICAL ABSTRACT

The generation of IgE to an antigen goes along with a concentration-dependent unresponsiveness of FcεRI+ cells to this antigen. Some non-covalent drug-protein complexes represent so-called "*fake antigens*" which can react with and crosslink preformed drug-specific IgE

1 | INTRODUCTION

Drug hypersensitivity reactions (DHR) are immune or inflammatory reactions elicited by a small molecule and occasionally proteins. DHR can be sub-classified as a specific immune reaction against the drug acting as antigen with drug-specific stimulations of antibodies or T cells (*drug allergy*), as off-target pharmacological activity of drugs with immune receptors (human leukocyte antigens, HLA or T-cell receptor for antigen, TCR) leading to T-cell–mediated immune stimulations (*p-i-concept*) and as pseudo-allergic reactions where the drug therapy results in activation of inflammatory cells or mediators without the involvement of the specific immune system ("*pseudo-allergy*").[1]

The clinical picture of DHR is very heterogeneous as different cell types (T cells, mast cells [MC], basophils, eosinophils, neutrophils, etc) and inflammatory mechanisms are involved.[2-4] This report focusses on IgE-mediated adverse reactions to small molecules, normally <1000 D. They represent an uncommon, but potentially dangerous complication of drug therapy. Symptoms appear rapidly after drug exposure in previously sensitized subjects and include generalized urticaria, angioedema, bronchospasm, and anaphylaxis with respiratory and/or gastrointestinal symptoms, cardiac arrest, and even death. Indeed, drug-elicited anaphylaxis is considered to be particularly dangerous with a high rate of deadly outcomes.[5]

The underlying mechanism of IgE-mediated drug allergy is based on the hapten concept. It was developed more than 80 years ago by Landsteiner et al,[6] stating that small molecules like drugs or other chemicals are too small to function as antigen for the immune system. Only if the drug acts as a "hapten" and binds to a protein and thus forms a larger drug-protein adduct, it functions as antigen to which immune reactions, including IgE, may develop. This hapten-protein (or hapten-carrier) concept relies on the ability of the drug (or metabolite) to bind via *covalent* bonds *stably* to a protein. The immunity may persist for years after stopping therapy. Importantly, the potentially severe symptoms mentioned above do not happen during the sensitization and only may become apparent through a new exposure/re-challenge.

This hapten-carrier concept was validated in an endless number of experiments. It was used to investigate immunity in animal models of autoimmunity, cancer immunology, allergy, and specific immunity to small molecules, etc. It also served as an explanation

for IgE-mediated drug allergy in the clinic: For example, allergy and clinical manifestations after beta-lactam therapy were explained by the hapten-carrier concept.[7]

Since only haptens were considered as potential elicitors of drug allergy, drugs in development were assessed for their ability to covalently bind to proteins.[8,9] To reduce the risk for DHR, only the development of drugs *not* capable of forming covalent bonds with proteins was pursued. Nevertheless, drug-induced allergy and in particular IgE-mediated anaphylaxis remained a substantial clinical problem. Anaphylaxis to beta-lactams, to proton-pump inhibitors (PPI), to neuromuscular blocking drugs (NMBA), to disinfectants like chlorhexidine, to radiocontrast media (RCM), and many more still occur.[2,7,10,11] Additionally, other ways of mast cell stimulation and degranulation by drugs were recently described, such as reactions triggered by mast cell-specific G protein-coupled receptors (MCGPR).[12]

A critical evaluation of patients with IgE-mediated allergy/anaphylaxis to drugs reveals some inconsistencies in the prevailing concepts, in particular regarding the symptoms during re-challenges: many of the drugs causing anaphylaxis are per se not haptens, but inert chemicals, not able to form covalent bonds; some might have acquired hapten characteristics by metabolism (eg sulfamethoxazole).[13] Most importantly, some of the reactions occur very fast before enough local concentrations of covalent conjugates can be formed. Of note as well, the immediate reaction in skin tests or a positive in vitro basophil activation test (BAT) to an inert drug cannot be explained by the hapten concept. The involved drugs are not "haptens"—leaving open how cross-linking of specific IgE, MC degranulation, and symptoms of IgE-mediated reactions are elicited by the drug.[1]

This paper addresses some of these inconsistencies comparing clinical observations to accepted features of IgE-mediated reactions. Such observations comprise the rapidity of the appearance of symptoms, in vitro and in vivo diagnosis of drug allergy, experience with desensitizations, pharmaceutical features of drugs, and speed of covalent vs non-covalent drug binding to proteins. The result is *a new interpretation of IgE-mediated drug allergy*: It extends the hapten concept and postulates: (a) When IgE is induced, the antigen simultaneously induces an MC unresponsiveness; (b) Some non-covalent bindings of drugs to proteins are affine enough to allow IgE cross-linking by the formed complexes; (c) the formation of covalent hapten-protein adducts in vivo is slow and may allow MC unresponsiveness both during sensitization and even during re-exposure: No symptoms occur.

The new concept is radical as covalent hapten-protein adducts are considered to be "good" (controlled) antigens, which, although they induce an unwished immunity, do simultaneously induce MC unresponsiveness. In contrast, non-covalent drug-protein complexes are taking the role of "fake antigens" responsible for harmful effects. The consequences of this new interpretation are potentially wide-reaching both for IgE-mediated drug allergy but also for IgE reactions and symptoms in general.

2 | DRUGS AND THE IMMUNE SYSTEM

2.1 | Non-covalent precedes covalent interaction between drug and protein

Small molecules like drugs bind to proteins, for example, human serum albumin (HSA). The attachment of a drug to a protein occurs first via non-covalent bonds (Table 1 and Figure 1).[14-16] These are the dominant type of intermolecular forces in supra-molecular chemistry and rely on van der Waals forces, electrostatic interactions, ion pairs, and hydrogen pairs. Even though they are weak individually, their cumulative energies of molecular interactions can be significant. The bindings are formed very rapidly, are reversible and the molar concentrations of the protein [P], ligand [L], and complex [LP] respectively are determined by the dissociation constant: $K_d = [L][P]/[LP]$. Thus, the affinity of interaction and the concentrations of drug and protein determine the number of complexes formed.

After an *initial* non-covalent binding, the drug may bind by a covalent bond to a certain amino acid within the protein (Figure 1). This feature depends on the chemical property of the drug. Other drugs cannot bind directly, but gain this property by metabolism.[13]

TABLE 1 Covalent hapten-protein adducts and non-covalent drug-protein complexes

Covalent bonds between hapten and protein (hapten-protein adducts)		Non-Covalent bindings between drug and protein (drug-protein complexes)
Stable	**Stability**	Reversible
High affine	**Affinity**	Low to medium affine
Mostly >20 min to hours	**Duration**	Very rapid <5 min
The stable hapten-protein adduct is a newantigen & is stimulatory for T and B cells	**Stimulation behavior**	As labile drug-carrier complex it is not a (true) antigen & not stimulatory for B and T cells, but may be able to interact with preformed IgE
The slowly increasing formation of hapten-carrier adducts allows induction of unresponsiveness of mast cells: No symptoms appear	**MC unresponsiveness**	The rapid formation of increase of protein complexes able to bind to preformed drug-specific IgE (=fake antigens) may overcome MC unresponsiveness and elicit MC degranulation with symptoms of anaphylaxis

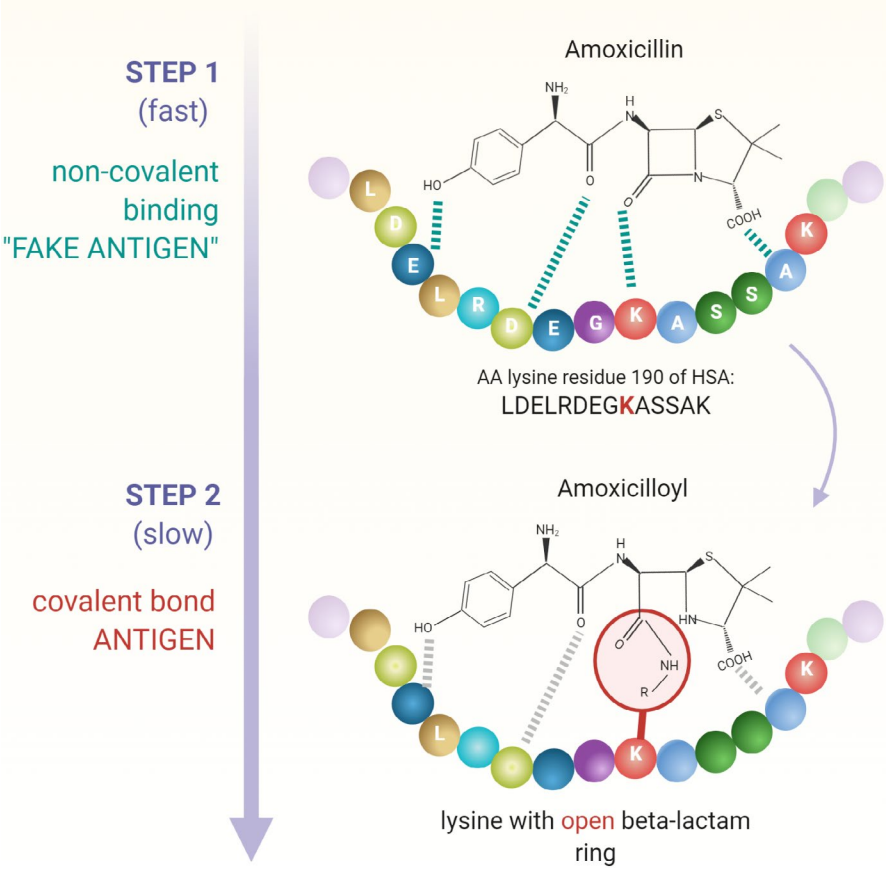

FIGURE 1 Non-covalent and covalent drug binding to protein. Typical examples of drugs acting as haptens are beta-lactams like penicillin G or amoxicillin. Their beta-lactam ring conjugates spontaneously to lysine groups within proteins. For example, amoxicillin binds first via non-covalent interactions to certain regions of the protein. These initial and fast non-covalent bindings positions the drug favorably to facilitate subsequent covalent binding of the beta-lactam to lysines: The beta-lactam ring opens and binds as amoxicilloyl covalently to lysins in position 190, 432, 525, 541 of the human serum albumin (HSA).[17] The configuration of the bound amoxicillin-HSA (non-covalent) and amoxicilloyl-HSA (covalent) is similar/identical for the reactive IgE antibody

A drug or drug metabolite able to bind by covalent bonds to a carrier molecule/protein is called a hapten. Covalent bonds involve the sharing of electron pairs between atoms. The formation of such bonds depends on the drugs involved. It may take minutes to hours. Studies with penicillin revealed[17-19] that under optimized in vitro conditions (pH 10.2), the first bond of a beta-lactam like penicillin G (as penicilloyl or penicillenic acid) tolysine 199 of human serum albumin (HSA) can be observed at 20 m inutes. At physiological pH 7.4, bonds are seen after 60 minutes or later and the process continues in the following hours. It is not readily reversible. The resulting hapten-modified protein ("adduct") represents a new antigen, to which an immune response can be developed.

Of note, the drug-protein complexes or adducts based on non-covalent or covalent bindings have a very similar "appearance," as the location of binding and the orientation of the drug vs protein may be the same in non-covalent and covalent bindings.[14] Consequently, an antibody initiated by the covalent hapten-protein adduct may recognize both, the complex formed by covalent bonds and the complex formed by non-covalent bindings (Figure 1). In this context, it is interesting to note that some drug-specific IgE can recognize the drug in the context of different proteins or even alone—as soluble drugs were able to inhibit the binding of specific IgE to drug-carrier adducts.[20,21]

2.2 | Drug-protein adducts based on covalent bonds are necessary to stimulate the immune system

To initiate an IgE-immune response to a small drug-like a beta-lactam, a complex interplay of antigen-presenting cells (APC), T cells, and B cells takes place.[1,7] Moreover, the provision of some danger signals may be needed.[22] Here, I focus on the antigen features of the drug-protein complexes.

Neither the drug itself (too small) nor the protein (often a self protein, to which tolerance exists) has antigen features. It is the newly formed hapten-protein adduct, which represents the antigen, which stimulates B and T cells. For T-cell stimulation, the hapten-protein adduct is processed inside APC into smaller peptides and then presented on HLA.[23] These immunogenic peptides keep the drug bound to the amino acid only if the bonds between peptide and drug are covalent and stable.

For instance, amoxicilloyl-albumin is taken up by dendritic cells (DC) and/or B cells acting as APCs.[7] This hapten-protein adduct is processed inside the APC to peptides. Due to the covalent link between the hapten and protein/peptide, the peptides resulting from processing and presented to T cells still carry the amoxicilloyl group.[23] A non-covalent bond between drug and protein would be disrupted by intracellular processing. This presentation of new (drug-modified) peptides stimulates T cells, which secrete IL-4/IL-13

to provide help for B-cell maturation into IgE-producing plasma cells. The secreted specific IgE binds immediately to the high-affinity Fc receptor for IgE (FcεRI) on mast cells (MC) and basophils, the individual is sensitized (Figure 3). But even if therapy is continued, no symptoms appear.

2.3 | During sensitization (IgE), desensitization of IgE/MC reactivity to the hapten-carrier complex develops

A cornerstone of the new interpretation of (drug) allergy is the hypothesis that the sensitization of MC by a *gradual* increase of specific IgE in the presence of antigen reduces MC reactivity to the specific antigen[1] (Table 2, Figure 2). The underlying mechanism of this *antigen-specific unresponsiveness* is not clear. It could be similar or identical to the process of drug desensitization: In in vitro models, it has been shown that this antigen-specific process blocks calcium flux, impacts the antigen/IgE/FcεRI complex internalization, and prevents the acute and the late-phase reactions as well as mast cell mediator release.[24-26] Importantly, this unresponsiveness of MCs is specific for the antigen-IgE complex, while MC reactivity to other antigens by IgE cross-linking persists. The MC unresponsiveness just covers the antigen concentration used for inducing unresponsiveness, normally determined by the serum concentration of the drug. When the MCs that carry specific IgEs are confronted with a suddenly higher concentration of specific antigen than the tolerizing dose, the unresponsiveness of MCs is broken and the MCs react/degranulate. This phenomenon is known as "breakthrough reaction" in drug desensitizations. It occurs, when the last increase of the drug concentration was too large.[27] When no antigen exposure occurs, this MC unresponsiveness is decreasing over time and an allergic reaction may re-appear to previously tolerated antigen concentrations: MC unresponsiveness can be re-adjusted by a natural exposure: For example, the first bee stings in spring in already sensitized beekeepers may cause urticaria, but these generalized reactions to stings disappear in the following weeks (Table 2)[28] and may also disappear by intended antigen exposure ("immunotherapy").[28,29]

Importantly, this MC unresponsiveness may represent the *normal* response when IgE is formed to protein antigens (allergens) and the antigen is still present (Table 2). It is different from the long-lasting T-cell–based tolerance mechanism,[30] as it is based on the unresponsiveness of MCs and probably also basophils, both carrying IgE-FcεRI.[24-27] The concept of MC unresponsiveness also implies that at least one scope of allergen-specific IgE is to react via MC to a *locally* relatively high allergen concentration, but *not* to normal, systemically available levels of allergen.

MC unresponsiveness could also explain the high number of sensitized but not allergic individuals in various studies on the prevalence of allergic diseases.[31] Sensitization is often identified by positive skin tests (prick, i.d.), where locally an excess amount of allergen is applied.[32] The concentrations used for skin tests break MC unresponsiveness and results in a local wheal and flare reaction. Since epidemiological studies revealed that about half of the skin test-positive individuals do not show symptoms to pollens (seasonal rhino-conjunctivitis), they may be unresponsive to the usual concentrations of pollen allergens reaching the tissue.[32,33] However, they react to the high local allergen concentrations applied in skin tests.

TABLE 2 Examples where the presence of IgE and antigen elicits no reaction

Fact	Explanation
Drug tolerance during initial IgE sensitization	During an, for example, 10 d therapy with amoxicillin, no symptoms appear, although specific IgE is already formed and MC are sensitized
Bee keepers tolerate bee stings when they carry IgE to bee venom	Bee keepers with IgE (and often IgG) to bee venom react with urticaria and (often mild) anaphylaxis in spring after the first bee stings, which subsides as the season carries on[28]
Bee or wasp allergic individuals tolerate 50 μg venom already after 3.5 h of immunotherapy[23]	Protocol: S.c injection of increasing concentrations of venom (0.1-1 μg, 10-20 μg, 30 -50 μg (>111 mg) within about 3.5 h. Transient MC unresponsiveness is achieved in IgE-sensitized individuals after 3.5 h with a tolerance of 50 μg venom; further injections (100 μg) are well tolerated at day 7, 21[28,29]
Drug desensitizations can be achieved within a few hours	Multiple schemes of desensitizations of IgE-mediated reactions to drugs exist.[27] Desensitization is achieved by starting with very low drug concentrations and increasing stepwise (30 min intervals) until the normal daily drug dose is achieved in 4-6 h. This desensitization is tolerated without symptoms. It is repeated after ca. 4 wk before the next drug therapy
Sensitization without symptoms in spite of allergen exposure is frequent	Many sensitized individuals (IgE, skin test reactivity) do not show allergy symptoms. For example, in the pollen season, the sensitized but not allergic individuals tolerate the pollen exposure without symptoms (ca. 20 μg inhaled major allergen/season). The skin tests are positive, as the local allergen concentration in skin testing is high (also ca. 10-20 μg/mL major allergen)[31,32]

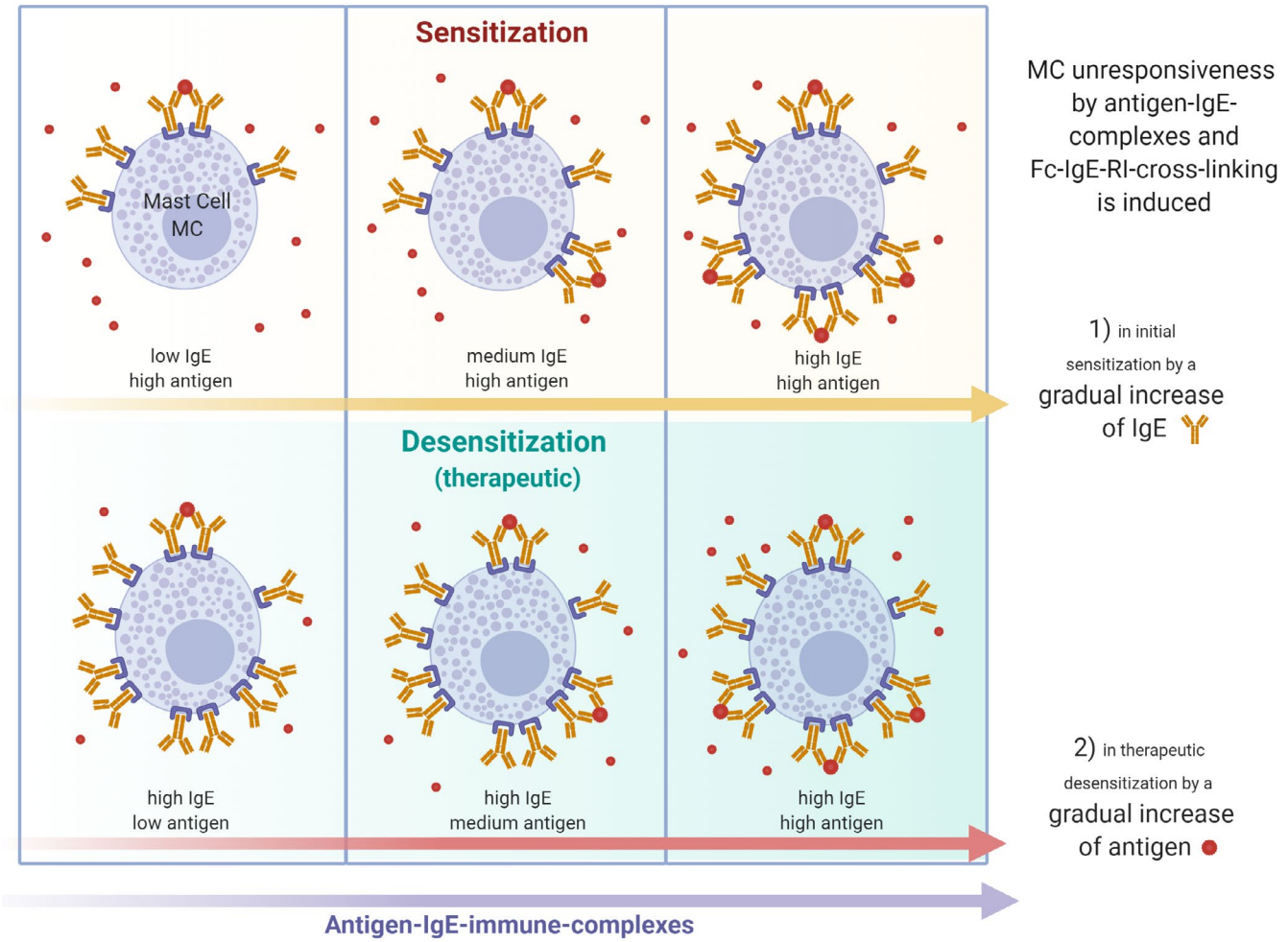

FIGURE 2 Induction of mast cell unresponsiveness by IgE-antigen complexes. During **sensitization** with hapten-carrier adducts, a gradual increase of drug-specific IgE occurs, which binds to FcεRI on MC. The MC bound specific IgE binds the hapten-carrier adducts. The slow increase of IgE and IgE-antigen complexes leads to a gradual desensitization of mast cells, which is specific for this antigen/allergen. In initial sensitization, the limiting factor is IgE. In already sensitized MC with already high specific IgE, the procedure of **"desensitization"** occurs by using initially low antigen (drug) concentrations. The limiting factor would be the antigen/drug concentration. In both, sensitization and desensitization, the slow process of antigen formation based on covalent bonds may also contribute to MC unresponsiveness (see text)

This suggests that the difference between allergic (sensitized and symptomatic) and sensitized (but asymptomatic) individuals is that the amount of allergen reaching the tissue is higher in allergic individuals. More likely seems that in allergic individuals, the IgE-coated MC reacts to lower local concentrations of allergen; IgE-mediated allergy is thus (a) defined by the formation of antigen-specific IgE, and (b) the MC (un)responsiveness to the antigen/allergen reaching the tissue is not well adjusted.

2.4 | Drug-protein complexes based on non-covalent bindings can cause degranulation of sensitized MC

The necessity of covalent bonds between drug and protein is a prerequisite for initiating an immune response to the drug/hapten, both in animal models as well as in humans. It is also observed for eliciting a MC degranulation in previously sensitized animals using in vitro prepared hapten-protein adducts. However, it has not been established, whether a non-covalent bound complex is sufficient for interaction and cross-linking specific IgE in already sensitized animals or not. One reason might be that the experiments with relatively labile drug-protein complexes did not deliver consistent, reproducible results and were dismissed. It is an exception that the non-covalent binding between drug and protein reaches an affinity which makes cross-linking of IgE/FcεRI possible.

The main arguments for the role of non-covalent drug-protein complexes in drug re-exposure reactions are summarized in Table 3. The formation of drug-protein adducts takes time, normally >20 minutes to hours, while symptoms appear more rapidly. Indeed, the rapidity of symptom appearance is a hallmark of anaphylaxis: first symptoms like local itching and erythema can sometimes be observed quasi immediately, soon after an injection was started. Generalized reactions of anaphylaxis occur often <5 minutes after

starting the exposure. Immediate skin test reactivity to drugs like beta-lactams starts <15 minutes after application, before covalent binding between beta-lactam and protein takes place.[17-19] Also the in vitro reaction in BAT is observed <5 minutes after combining drug and basophils. These clinical and laboratory observations are hard to reconcile with a need of prior formation of drug-protein adducts to generate a functional antigen. On the other hand, some rather rapid formations of covalent bonds have been reported for some drugs.[34-36] Although such reactions seem to be the exception and not the rule, it is clear that a more precise analysis of the non-covalent drug-protein bindings, their affinity, and in vivo conditions are needed to substantiate the postulated role of non-covalent bindings in re-exposure reactions to drugs.

For some drugs, metabolism is required to form the reactive metabolite: A well-investigated example is sulfamethoxazole (SMX). It is metabolized in the liver to sulfamethoxazole hydroxylamine (SMX-NHOH), which is further oxidated in the tissue to the reactive hapten SMX-NO, able to undergo covalent bonds.[13] This metabolism lasts >6-10 hours.[13] But skin test reactivity and in vitro BAT can be observed within 15 minutes with SMX itself, which does not have hapten characteristics. The IgE detected was probably generated against SMX-NO and is cross-reactive with the non-covalently

TABLE 3 IgE Reactivity and cross-linking by non-covalent drug-carrier complexes

Positive skin prick tests (SPT, within 15 min) to amoxicillin, cefuroxim, etc, before covalent drug-carrier complexes are formed
Positive SPT/i.d. tests to drugs (15 min) like sulfamethoxazole, which per se does not form covalent bonds; SMX needs **metabolism** to generate reactive metabolites (SMX-NO), which needs >6-10 h[13]
Positive BAT to drugs: It occurs fast, before covalent bonds are formed (amoxicillin, cefuroxim, etc) or reactive metabolites (eg SMX-NO) are generated in the in vitro conditions
Anaphylaxis with mast cell degranulation to drugs occurs <5 min after injection, before covalent links can be formed; first local symptoms (itching, erythema) may occur already during the injection (1-2 min)

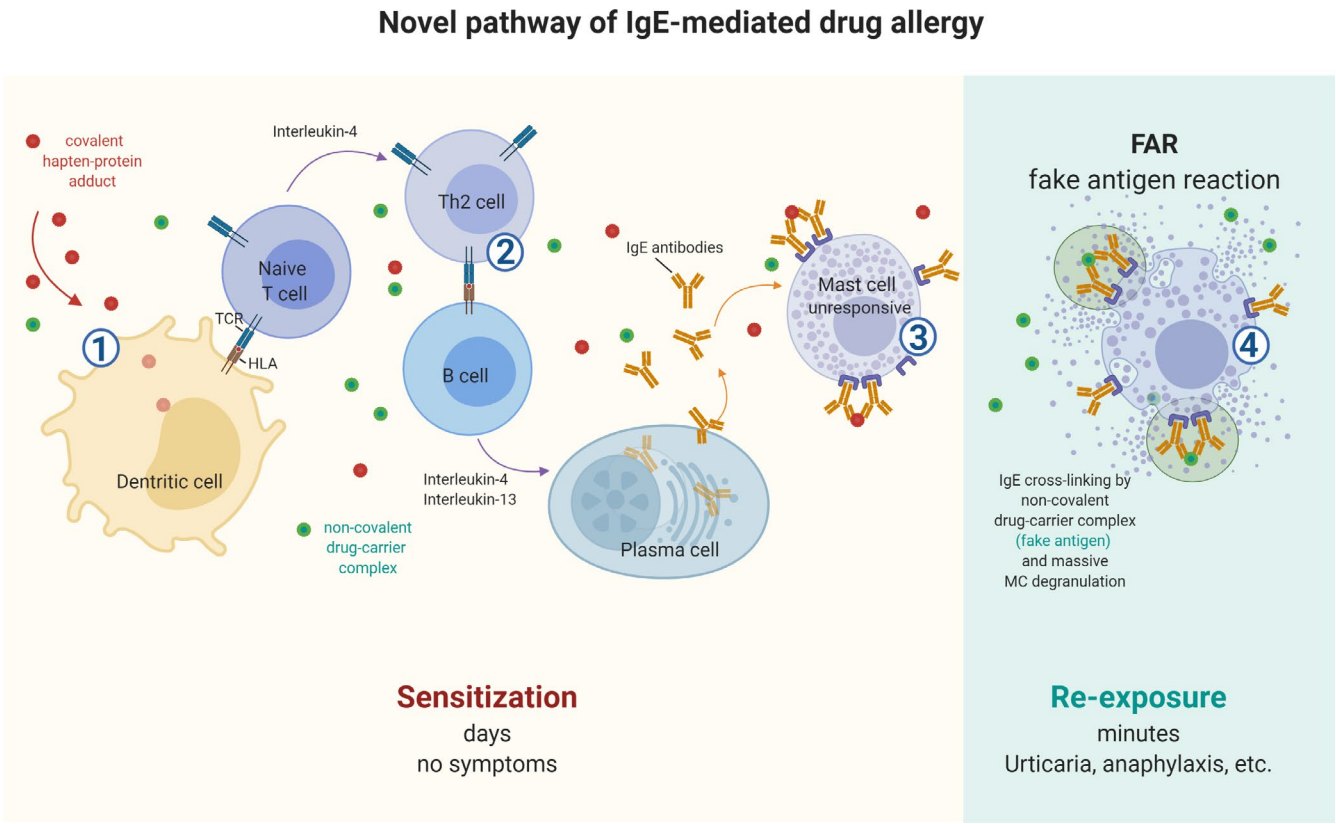

FIGURE 3 Induction of IgE and MC unresponsiveness by hapten-protein adducts and of MC degranulation by fake antigen. ① Covalently bound hapten-carrier adducts(=true antigen) are taken up by APC like DC, processed and presented as drug-peptide on HLA to T cells. Some specific T cells react and secrete cytokines like IL-4, IL-13 ②, which booster B-cell maturation to plasma cells secreting hapten-carrier specific IgE. These IgEs bind to high-affinity FcεRI on mast cells (MC), where they are cross-linked by hapten-carrier complexes. The increasing amount of immune complexes (hapten-carrier/IgE antibodies) interacting with FcεRI make MC unresponsive ③ to the specific antigen. The sensitization phase remains asymptomatic, although antigen (continued use of drug), IgE, and mast cells are present. After a drug-free interval,the patient may be re-challenged by the drug ④: Some drugs are able to form non-covalent drug-carrier complexes rapidly and in high amount ("fake antigens"); they look similar/identical to true antigen and can bind to the preformed drug-specific IgE on MC: the quasi immediately and ubiquitously available, large amount of fake antigen can overcome MC unresponsiveness and elicit a generalized MC degranulation with anaphylaxis

bound SMX used in skin tests or BAT. Such a cross-reactivity between SMX-NO and SMX has already been observed in T-cell reactions to SMX and SMX-NO.[37]

2.5 | It is all about drug-protein binding: fake antigen in drug allergy

A comparison of covalently and non-covalently linked drug-protein complexes points out that the *nature* of drug-protein binding may determine whether "*silent" immunity* or *symptomatic allergy* evolves.

Hapten-protein adducts, based on covalent bonds, represent novel antigens, which can induce a complex immune response, including IgE. IgE reactions are not per se "harmful," even if we associate them with the very common, annoying allergies. The first encounter with the antigen is often unspectacular and sensitization remains unnoticed since sensitization goes along with MC unresponsiveness. In most IgE reactions, this tight control may persist and no symptoms appear.

Not only the induction of immune response but also the reaction at re-exposure may be mitigated by the type of antigen. The formation of covalent bonds is a comparatively slow process, and for some drugs, even a metabolic step is intermingled, before complex formation can start. Moreover, the number of antigenic epitopes is limited to those protein sites able to accommodate covalent binding, while non-covalent bindings may occur on more sites, including some where no covalent link is possible. Thus, if the IgE reactivity is directed to haptens exclusively, not only the formation of antigen complexes is slow (hours) but also the amount of antigenic sites is limited. Both conditions would favor the induction of MC unresponsiveness at re-exposure again and no symptoms would occur.

The situation is different if the non-covalent drug-protein complexes are

1. Relatively stable,
2. Can interact with preformed IgE, and
3. Even cross-link the FcεR-bound IgE.

Such complexes *pretend* to be relevant antigens but are in reality "**fake antigens**." They are formed very rapidly and in high concentrations (see Table 3) and thus overrule MC unresponsiveness: an uncontrolled MC degranulation/**"fake antigen reaction" (FAR)** with urticaria, angioedema, and anaphylaxis may occur (Figure 3; Box 1).

2.6 | Fake antigens and FAR/anaphylaxis

It is unclear what the clinical benefit of anaphylaxis may be. Perhaps there is none, and systematic MC degranulation is not a valuable option in immune defense as it should not happen. If it occurs, it may be by mistake, as the immune system recognizes a fake antigen as a true antigen.

Box Fake antigen

The term *fake antigen* is novel and needs some explanation. I use it to describe certain drug-protein complexes, which have two features: a) they are formed by relatively stable, *non-covalent* bindings between drug and protein and b) are able to interact with preformed (drug specific) IgE and cross-link IgE on FcεRI expressing cells. As they are unable to induce a drug-specific immune response, they are not formal antigens per se, they are a *fake*. Nevertheless, such *fake antigens* can appear rapidly and in high amounts and are able to elicit deleterious effects.

Consequently, drugs or drug metabolites causing anaphylaxis (eg beta-lactams, quinolones, chlorhexidine, metamizole, muscle relaxants, PPI, RCM, SMX/SMX-NO, etc) are characterized by two features:

1. Ability to bind covalently to proteins and to form an antigen, which is needed to induce IgE;
2. Ability to form a sufficiently affine non-covalent complex (*fake antigen*), which reacts with and cross-links the preformed IgE.

In up to 50% of patients with drug-induced anaphylaxis, a prior exposure to the drug is not documented ("anaphylaxis at first sight")[2,11]: some reactions might be IgE independent.[12] Even if IgE was involved, the IgE might have been induced by a compound, which is different from the newly formed fake antigen eliciting anaphylaxis, as the IgE is just cross-reactive. Under these special conditions, even a drug, which is per se *not* able to form an antigen and to induce IgE, may cause anaphylaxis.

The following conditions may additionally favor anaphylaxis by fake antigens (FAR): providing a high amount of drug; this may compensate for moderate affinity (Ka); and administration of the drug by bolus injection. The short-lasting, high drug concentration may generate a tsunami of fake antigen; examples for highly dosed and fast-delivered drugs causing anaphylaxis (often at first sight) may be RCM or NMBA.[2,12]

Since fake antigens can bind and cross-link IgE/FcεRI, they could also be used for desensitization to induce MC unresponsiveness: However, they need to be applied very cautiously, in small, stepwise increasing concentrations to avoid anaphylaxis-related side effects. It is uncertain, whether the duration of induced MC unresponsiveness caused by fake or true antigen differs.

In this context, one should re-consider the meaning of DHR diagnosis by immediate skin tests (prick, i.d.) as well as by the in vitro basophil activation tests (BAT) (Table 3) using the drug alone: Both tests rely on drug-specific IgE and FcεRI cross-linking and are evaluated within 15 minutes. Although both tests need to be interpreted

with caution, as they may be false positive for various reasons, *these tests detect in principle the ability of the drug to form a fake antigen*. They do *not* detect reactivity to the hapten-protein adduct. In contrast, a serological assay like "ImmunoCAP" just detects drug-specific IgE but does not give indications on the ability to elicit a FAR.

The occurrence of atopic allergies like pollinosis and allergic asthma is not associated with drug allergy.[38] Only the clinical manifestation of drug allergy symptoms might be aggravated in acute drug allergy, for example, if anaphylaxis involves the lung in a patient with allergic asthma. One might conclude that the regulation of MC unresponsiveness is not impaired in patients with drug allergy and that the clinical problems of immediate drug allergy are mainly due to the sudden formation of fake antigen.

3 | CONCLUSION

DHRs are interesting diseases on one hand, as the eliciting cause (drug) is well defined with exact data on dose, duration of exposure, availability, kinetic, metabolism, and serum concentrations in humans. On the other hand, DHR is clinically difficult. It occurs only rarely and unexpectedly, and many reactions may represent an exception and not the rule. As iatrogenic diseases, they are hard to reproduce for ethical reasons. Additionally, some DHRs are a result of a series of weak non-covalent and reversible reactions, but not of a very strong, quasi irreversible, covalent reaction. Moreover, and maybe partly because of this, for most DHRs we do not have animal models.

The methodological approach taken in this paper is unusual: The novel conclusions and alternative explanation of IgE-mediated drug reactions are based on well-known facts and neglected inconsistencies. Here clinical observation and history, skin and in vitro tests, pharmacological features of drugs, their protein-binding ability and immunological concepts of IgE response are combined to confirm the old dogma that only covalent drug-protein complexes can *induce* IgE. But the *effector* phase, which is elicited by IgE and MC, cannot be reduced to antigens formed by covalent bonds. When considering the different kinetic of forming non-covalent drug-protein complexes or covalent hapten-protein adducts, the speed of clinical reactivity, particularly of anaphylaxis, and insights from drug desensitizations, a new concept of IgE-mediated drug reactions emerges: It's three main concepts are summarized in Figure 3:

1. Inducing IgE goes along with silencing MC reactivity to the same antigen. This is a natural and normal process in IgE-mediated reactions, both for drugs, but also for normal protein allergens. It combines non-reactivity of IgE-coated mast cells to small concentrations of drug/allergen while permitting reactivity to high local levels.
2. At re-exposure, anaphylaxis-causing drugs form fake antigens fast and in high quantity. They are dangerous as they can react and cross-link preformed drug-specific IgE and cause MC degranulation with urticaria/anaphylaxis.
3. If at re-exposure only covalent hapten-protein complexes react with drug-specific IgE, the reaction may remain asymptomatic, as the slow generation of such stable antigens may re-establish MC unresponsiveness.

The beauty of this concept is its simplicity. The involved components are drug concentrations, type of bonds(covalent or non-covalent), and affinity of drug-protein bindings: together they result in a slow or fast formation and ±high amount of drug-protein complexes, which then determine MC unresponsiveness with silent immunity vs MC reactivity with allergy.

It should be emphasized that part of the concepts proposed here apply to allergy in general. The IgE antibody is evolutionarily very old[39] and cannot and should not be seen from an allergy perspective alone. IgE may represent a normal, potentially beneficial immune response to *local antigen accumulations*. Anaphylaxis to drugs is a rare event, which only appears when various exceptional conditions occur together: some rely on the drug, others are due to the individual (eg prior exposure to IgE-inducing antigens, drug metabolism). The possible consequences of this new interpretation of IgE-mediated drug allergy would be far-reaching for the clinical practice, risk estimation, and prevention of drug allergy, and our concept of IgE-mediated allergy in general. It is hoped that these ideas promote discussions to further shed light on the topic, and consequently prompt new research confirming or disapproving the theories discussed.

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CONFLICT OF INTEREST

The author has nothing to disclose.

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