

Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept

Werner J. Pichler

Purpose of review

Drug allergies are examples of immune reactions to small molecular compounds. In many drug allergies drug specific CD4+ and CD8+ T-cells can be detected, which recognize small chemicals via their $\alpha\beta$ -T-cell receptor in a major histocompatibility complex dependent way. In this review a new concept of drug presentation to T-cells is presented.

Recent findings

Drugs were stimulatory for T-cells if they bound covalently to peptides or proteins, but also if the drug had structural features allowing it to bind in a labile way (noncovalently) to the major histocompatibility peptide complex. This latter binding method has some similarities to superantigen stimulations and can explain allergies to drugs that are not metabolized. It has been described in patients with maculopapular, bullous and neutrophilic drug eruption, as well as in contact dermatitis.

Summary

Noncovalent drug presentation leads to the stimulation of immune cells, namely T-cells. The drug needs two surface molecules (one inert serving as a scaffold, major histocompatibility complex, and one reactive, T-cell receptor) to exert its function. Although two receptor structures are involved, the process is reminiscent of a pharmacological interaction between a drug and its receptors and, from the phrase pharmacological interaction with immune receptors, was thus termed the p-i concept.

Keywords

drug hypersensitivity, T-cells, drugs, T-cell receptor

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Division of Allergology, Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, University of Bern, Bern, Switzerland

Correspondence to Werner J. Pichler, Inselspital, CH-3010 Bern, Switzerland; e-mail: werner.pichler@insel.ch

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Abbreviations

MHC	major histocompatibility complex
p-i	pharmacological interaction of drugs with immune receptors
TCR	T-cell receptor
MPE	maculo-popular exanthema

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Introduction

Small chemical compounds gain immunogenicity by binding to larger molecules (hapten carrier concept). As the binding can occur to many different structures, namely soluble proteins, cell bound proteins (e.g. adhesion molecules, cellular receptors) and even the major histocompatibility complex (MHC)-molecules themselves, the ensuing, hapten-specific immune response can be very heterogeneous, which is also reflected in a great heterogeneity of distinct clinical symptoms.

The multitude of immune reactions that develop against small compounds might also explain why in the past the study of hapten-specific immune reactions provided a constant source of new insights into general principles of immune reactions. For example, the concept of cellular immunity was actually developed by studies made with small chemicals causing contact dermatitis [1]. In addition, one of the first descriptions of MHC-restrictions of T-cell mediated immunity was based on experiments using trinitrophenyl-modified cellular structures [2]. The better insights made into the mechanisms underlying distinct clinical presentations of drug allergies continue to challenge prevailing concepts of immune responses [3•].

Hapten and prohaptent concept

Until recently the hapten model was the only concept explaining the recognition of small chemicals like drugs (mostly <1000 D) by the immune system [3•–5]. It implied that a small molecule is too small to be recognized by the immune system. Covalent binding of a drug or chemical to proteins modifies the latter and renders this newly generated hapten-carrier-complex immunogenic to the immune system. These hapten-modified structures can be recognized by immunoglobulins, or, after processing to small peptides and presentation on MHC molecules, by T-cells. However, T cell recognition can only occur if the modification affects the part of the protein that is presented to the immune system on MHC molecules as a 9–14 amino-acid peptide.

Most drugs are, however, chemically not reactive and thus lack hapten like features. Nevertheless, some of them still elicit allergic side effects. It has been hypothesized that, in these cases, drug metabolism may lead to metabolites that are chemically highly reactive and thus behave like haptens and modify

proteins covalently [4–8]. Some of these metabolites remain elusive as they are not stable and bind immediately to proteins; or they might be inactivated rapidly outside or inside of the metabolizing cells by, for example, glutathione. Alternatively, they bind to proteins, but do not elicit an immune response. The reason for this ‘ignorance’, which seems to be the predominant type of immune response to most drugs, might be the missing activation of the innate immune system, as normally provided by bacteria or viruses which activate antigen presenting cells e.g. by binding to TOLL-like receptors [6]. In the absence of such a danger signal, the immune system may not react [5].

Other drugs might be metabolized to more stable intermediates. An interesting example is sulfamethoxazole, whose metabolism has been well analyzed [5,9]. It might be a typical example for a prohaptent, which gains its immunogenicity by intracellular metabolism. Whilst the drug itself is chemically not reactive, a cytochrome p450 dependent metabolism leads to sulfamethoxazole hydroxylamine. This compound is still not chemically reactive and can be found in the urine of sulfamethoxazole-treated patients [8]. However, a simple (extracellular) oxidation can transform it to sulfamethoxazole nitroso, a chemically reactive compound able to act as a hapten and to bind covalently to proteins or peptides [5]. Besides liver cells, other cells, such as keratinocytes, may also transform the drug to sulfamethoxazole hydroxylamine and generate this antigen locally, which might be an explanation for extrahepatic manifestations of drug allergy [9]. Similar concepts have been elaborated for other compounds, such as lamotrigine and carbamazepine [10,11]. These compounds are known to elicit so called drug (anticonvulsive) hypersensitivity, which is a severe drug allergy with high eosinophilia, often involving skin and causing rather severe liver cell damage [12,13]. Indeed, the prohaptent concept might be highly relevant for those drug allergies that go along with liver cell damage. It is well documented for tienilic acid [14].

The prohaptent concept has recently been experimentally supported by animal experiments: While immunization of rats with sulfamethoxazole failed to elicit an immune reaction, immunization with the hapten sulfamethoxazole-nitroso consistently elicited a B and T-cell immune response. However, if sulfamethoxazole was given in complete Freund’s adjuvant, the rats developed an immune response to the nitroso form but not to sulfamethoxazole. This clearly indicates that metabolism can give rise to a new antigenic structure and can elicit a metabolite specific immune response under special circumstances [15••].

On the other hand, the majority of T-cell clones obtained from three patients with sulfamethoxazole-

allergy recognized exclusively sulfamethoxazole and only few of the nitroso form [16]. Thus, in such patients, both an immune response to the inert parent compound and possibly also to the metabolite might develop. This would be compatible with the clinical observation, that sulfamethoxazole can elicit antibody and T cell mediated drug allergies, whereby the antibody mediated reactions would be due to the nitroso metabolite, which indeed is binding to proteins after SMX uptake [17].

A further interesting aspect of the prohaptent concept comes from consideration of its pharmacogenetic properties, which might explain individual susceptibility to developing drug hypersensitivity [18•]. The drug metabolizing enzymes are inherited in different allelic forms with distinct functional activities. Thus, dependent on the individual pharmacogenetic disposition, rapid or slow acetylation may occur or a higher or lower amount of a reactive metabolite might be generated, for example. In addition, the generation of a toxic metabolite might also provide some stimulation of the innate immune system [6] providing a so called ‘danger signal’ [19], which facilitates an immune response to the metabolite [5].

The pharmacological interaction of drugs with immune receptors concept

During the past years our group elaborated a new possibility for drug presentation, namely a pharmacological interaction of drugs with immune receptors, termed the p–i concept [20–22]. Chemically inert drugs, unable of covalently binding to peptides or proteins, can nevertheless associate with the MHC–peptide complex, albeit in a rather labile way (first step). The drug binding is easily removed by simple washing. In pharmacological terms, this means that the binding of the drug to the MHC–peptide complex has a low affinity, probably in the millimolar to micromolar range.

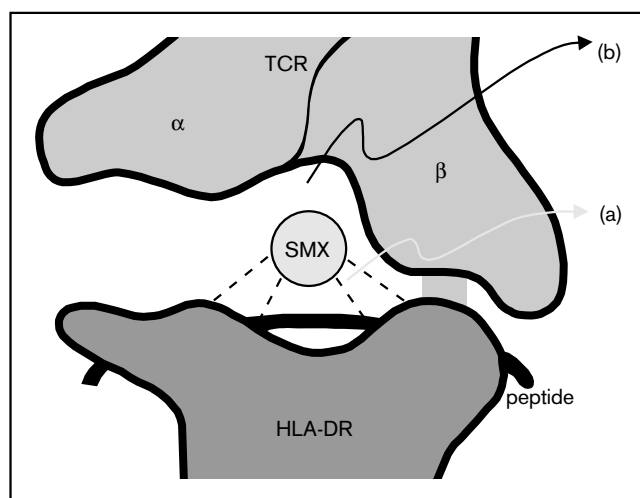
It is likely that this labile binding to MHC–peptide complexes is not stimulatory for the cell per se; but it may serve as a scaffold for a second receptor, namely the T-cell receptor (TCR) (second step). Part of the very heterogeneous pool of T cells with distinct TCRs may interact with this peculiar drug–MHC complex (Fig. 1). This TCR interaction can be of relatively high affinity [23,24•] and is capable of generating a receptor-mediated signal, which is interpreted as immunological, as a T-cell is reacting.

This p–i model has been demonstrated for sulfamethoxazole, lidocaine, mepivacaine, celecoxib, carbamazepine [20,22,25••,26,27•]. It is relevant for maculopapular drug eruption, erythema exsudativum multiforme, contact dermatitis, acute generalized exanthematous pustulosis

and was recently shown to be relevant for toxic epidermal necrolysis as well [27•] (Table 1). How (i.e. by van der Waals, hydrogen bonds) and where on the MHC–peptide complex the drug binding occurs is still unresolved.

There is good evidence that the type of peptide embedded in the MHC groove is not relevant for drug binding: alteration of the peptide by adding other peptides in excess did not alter the ability of the antigen presenting cell to present the drug (Burkhart *et al.*, in preparation). Even different human leukocyte antigen-DR alleles, which surely bear different peptides, are able to present the drug to certain T-cell clones. Thus, neither the type of peptide nor the MHC allele is a limiting factor for peptide presentation [22•].

Figure 1. The pharmacological interaction of drugs with immune receptors concept



A drug, such as sulfamethoxazole (SMX), binds to major histocompatibility complex (MHC)–peptide complexes (and probably to other molecules as well). This binding is of low affinity, and has no functional consequence (a). However, if a T-cell with a fitting T-cell receptor (TCR), on its way to screen the MHC molecules, passes by, a stabilization of the binding by this ‘sandwich’ may occur and the TCR transmits a signal to the cell (b). Thus, a pharmacological interaction with an immune receptor leads to cell activation, which is interpreted as antigenic stimulation, as only those immune cells react, which bear fitting TCRs. HLA, human leukocyte antigen.

Table 1. Clinical examples of noncovalent drug presentations

Drug	Clinical reaction
Sulfamethoxazole	MPE [16] Toxic epidermal necrolysis [27•]
Lidocain/mepivacain	Contact dermatitis [22]
Celecoxib	Acute generalized exanthematous pustulosis [25•]
Carbamazepin	Drug hypersensitivity syndrome
Ciproxin	MPE

MPE, maculo-papular exanthema

Differences between covalent and noncovalent drug presentation

A comparison of drug and peptide specific T-cell clones did not reveal differences in the kinetics of TCR activation [21]. On the other hand, drugs gaining immunogenicity by their hapten characteristics or by their ability to noncovalently interact with MHC–peptide complex differ considerably in two aspects: (1) Haptens are primarily immunogenic due to their chemical features. Their chemical reactivity enables them to stably modify proteins and peptides. In contrast, drugs, which bind in a labile way to MHC molecules, are immunogenic, based only on their structural features, which enables them to interact with immune receptors (MHC and TCR). This latter feature has not yet been considered in the development of a drug but may account for a substantial portion of unforeseen side effects [28•]. (2) The ability of a drug to bind to proteins, based on chemical or structural features, has a major impact on the type of immune reaction and consequently on the evolving clinical picture. A hapten-like drug (e.g. amoxicillin) is able to alter many different proteins, either soluble or cell bound, and it can even modify different MHC molecules and their embedded peptides directly; this may elicit seemingly all types of immune reactions. Indeed, penicillins are reported to cause different antibody mediated diseases, but also various T-cell mediated reactions. If the drug acquires immunogenicity only by labile binding to MHC molecules, the immune reaction will be restricted to T-cell but not B-cells. This model would explain exclusive T-cell reactions, as it is not infrequently seen with drug reactions. For example, carbamazepine is known to elicit maculopapular exanthema (MPE) and so called drug hypersensitivity syndromes, two typical T-cell mediated diseases, but not anaphylaxis.

Both labile and hapten like presentations of a drug might occur together and lead to distinct symptoms. This might be the case in sulfamethoxazole allergy, where the antibody immune response might be directed to sulfamethoxazole-nitroso, while the exanthems might be due to presentation of sulfamethoxazole itself.

Both types of MHC-dependent drug presentations, based on covalently or labile bound drugs, can elicit quite heterogeneous T-cell responses. It is still an enigma as to why the same drug, such as amoxicillin or sulfamethoxazole, elicits maculopapular exanthemy in one patient and a bullous skin eruption in another individual. Possibly the human leukocyte antigen allele or differences in the drug metabolism play a role [18•,25•,29•].

Similarities of the p–i concept to superantigen stimulations

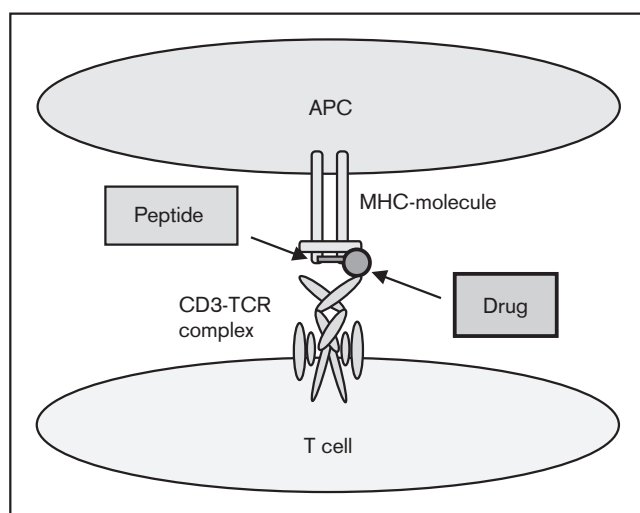
Drugs are peculiar antigens for T cells. They are clearly distinct from normal peptide antigens, but may have

some similarities to metals (nickel), which are well known contact-sensitizers and able to elicit T-cell responses [30,31,32]. On the other hand, there are some similarities to superantigens such as Staphylococcal enterotoxin B or toxic shock syndrome toxin-1, which may be also relevant for understanding some clinical symptoms [32] (Fig. 2): (1) Drugs, like superantigens, bind from the outside of MHC and TCR without the need for processing [20,21,22]. (2) Superantigens and drugs can be 'recognized' by T-cells after binding to different MHC alleles. While the majority of drug specific T-cell clones are human leukocyte antigen-allele restricted, there are exceptions to the MHC restriction of hapten specific T-cell responses [24*]. If the TCR is interacting with the drug (a hapten or an inert substance) in a high affinity manner, the binding energy provided by the interacting carrier molecules (peptide and MHC) is of minor importance. Under such circumstances the hapten specific immune response is not MHC-allele-restricted. This has been documented for penicillin G, trinitrophenyl and sulfamethoxazole responses [24*,33], and occurs, when the hapten binds in a central position of the peptide (amino acid at position four, five, six of the nine amino acid peptide) [33]. (3) In some instances, drug reactive T-cells show a use of a particular TCR-V β . Such an oligoclonal T-cell reaction *in vitro* could be observed with amoxicillin [34]. Oligoclonality, namely the rapid expansion of T-cells bearing certain TCR-V β elements, can occur during the

initial phase of a strong immune response (e.g. to HIV or Epstein-Barr virus peptides [35,36], but is also a typical feature of superantigen stimulations [32]. The occasionally observed oligoclonality of T-cell reactions to drugs is also reminiscent of nickel-stimulated T-cell cultures. Nickel (nickel sulphate), which is a common contact sensitizer, can preferentially stimulate T-cells expressing TCR-V β 17 [30]. It binds, like certain drugs, in a noncovalent way to MHC-peptide complexes. Nickel sulphate and drugs might thus share some common features in the way they stimulate T-cells. (4) There are also, however, some arguments against a direct comparison of T-cell stimulations by drugs with those by superantigens. Drugs are far smaller than superantigens and are unable to consistently activate T-cells. A previous expansion of the responsive T-cell subset seems to be required to allow measurement of a reaction, and can also be observed *in vivo*, as the second response frequently occurs more rapidly. Moreover, no *in-vivo* data are yet available for such an oligoclonal T-cell reaction during an acute, severe drug allergy.

In summary, while drug stimulation may in certain circumstances be comparable with oligoclonal superantigen-like stimulations, the vast majority of drug specific T-cells actually show a heterogeneous TCR repertoire [23,34]. This implies that many different TCRs (TCR-V α and V β) can react with the same drug presented by MHC molecules, and that the stimulation of a certain TCR-V β by a drug is more the exception than the rule.

Figure 2. Similarities of superantigen and drug stimulation of T-cells



Some peculiar features of T-cell stimulations by drugs are shown, which are in agreement with superantigen stimulations. They include allele unrestricted presentation [22], CD8 reactions with major histocompatibility complex (MHC)-class II [20], oligoclonal T-cell receptor (TCR) V β expansion [34], stimulation of both CD4 and CD8 cells by the same 'antigen' [20,26], binding from the outside to the MHC-peptide complex [20,21] and a high incidence of alloreactivity [24*]. APC, antigen presenting cell.

Conclusion

The p-i concept of drug presentation postulates that chemically inert drugs can bind to MHC-peptide complexes and happen to fit into certain TCRs and thereby elicit an immune response. This manifests itself as drug allergy. This new concept can explain some peculiar, clinical features of drug allergy: an immune response to an inert substance, the manifestation of drug allergies in organs without known drug metabolism, the sometimes selective T-cell stimulation, without antibody response, the vigorous immune response to inert drugs *in vitro* or in skin tests. The process plays a role in different forms of drug induced exanthems. Since such reactions can elicit severe, life threatening side effects, the pharmaceutical industry should develop tests to predict the potential of drugs to interact with TCR based on structural requirements. The great variability of TCR seems to make such a prediction a 'heroic' undertaking. But the fact that the majority of side effects are due to a small group of drugs makes it likely that they have a certain motif, which fits into TCRs and could be elucidated. This could reduce such side effects and prevent the extremely expensive withdrawal of drugs from the market soon after their launch.

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