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Chapter 4

Physiology and Pathology of Drug Hypersensitivity: Role of Human Leukocyte Antigens

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Additional information is available at the end of the chapter

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Abstract

Drug Hypersensitivity reactions can be distinguished in adverse drug events and adverse drug reactions. They represent a major problem in the medical scheme, since they are often underestimated. Pharmacogenetic analysis demonstrated significant associations between emerging hypersensitivity reactions and distinct genes of the HLA complex. HLA-mediated hypersensitivity reactions particularly affect skin and liver, however, impairment of the bone marrow and kidney function could also be observed. These life threatening medical conditions can be attributed to the activation of autologous drug-specific T-cells. Severe drug hypersensitivity reactions that resemble acute GvHD are linked to certain specific HLA alleles. The most common hypersensitivity reactions occur after the treatment of HLA-B*57:01$^+$ HIV patients with abacavir and HLA-A*31:01$^+$ or B*15:02$^+$ epileptic patients with carbamazepine (CBZ).

Keywords: HLA, hypersensitivity, adverse drug reactions, T-cells, carbamazepine

1. Introduction

The administration of a drug can be accompanied by harmful adverse events such as gastrointestinal bleeding or skin rashes (**Table 1**). The classification of these adverse events is illustrated in **Figure 1**. Adverse events comprise all harmful reactions during drug application regardless of a causal link between the drug and the event. If the drug usage is causal for the symptoms, the condition is called adverse drug event (ADE) [1–3]. The term ADE comprises harm caused by the drug itself as well as harm caused by the use of the drug, for instance inappropriate dosages or premature discontinuation of the medication [1]. Mostly,

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Drug	Function	Symptoms of an ADE	Mechanism	Classification
Immunosuppressive	Suppression of the immune system	Virus infections	Immune system is not able to properly cope with the virus	ADE
Morphine	Analgetic agent	Unconsciousness, hypoventilation, miosis	Overdose	ADE
Antihistamines of the 1st generation	H1-receptor antagonist	Sedation	Crossing of the blood-brain barrier and off-target binding	Type A ADR
NSAIDs	Inhibition of the synthesis of proinflammatory prostaglandins	Gastrointestinal bleeding	Production of protective mucous in the stomach is decreased	Type A ADR
		Asthma, rhinitis, angioedema	Synthesis of leukotrienes, activation of the innate immune system	Pseudoallergic type B ADR
Penicillin/β-lactam antibiotics	Antibiotic drug	Urticaria, anaphylaxis, hypotension, bronchospasm, angioedema	Hapten-model, type I reaction	Allergic type B ADR
Methyldopa	Antihypertensive drug	Hemolytic anemia	Type II reaction	Allergic type B ADR
Aminopyrine		Leukopenia	Type II reaction	Allergic type B ADR
Minocycline	Antibiotic drug	DRESS	Type III reaction	Allergic type B ADR
Allopurinol	Uricostatic drug	SJS/TEN	P-i model, type IV reaction	Pharmacologic type B ADR
Abacavir	Antiretroviral medication	Rashes, fever, gastrointestinal and respiratory symptoms, malaise, lethargy, arthralgia, myalgia	Altered repertoire model, type IV reaction	Pharmacologic type B ADR
Carbamazepine	Antiepileptic drug	Maculopapular exanthema, DRESS, SJS/TEN	Altered repertoire model, type IV reaction	Pharmacologic type B ADR

Table 1. Examples of drugs leading to adverse events.

medication errors do not cause any harm in patients, but in some cases ADEs are triggered by increased or decreased drug doses [1]. Opioid-intoxication, as for example a morphine overdose leads to unconsciousness, hypoventilation and miosis. The probability of an ADE differs from substance to substance. The antimitotic nystatin is very unlikely to cause unwanted effects, since it is directed against a cell wall component of fungi and mycoplasma. In contrast, immunosuppressive medication has a high risk of enabling virus infections and diminishing the surveillance of cancer development as the down regulated immune system is no longer able to properly cope with the virus or neoplastic cells [4].

However, certain drugs can cause the patient harm despite proper application. Those unintended and harmful reactions to drugs at therapeutic levels are termed adverse drug reactions (ADRs) (WHO 1972). They are triggered by the drug itself and not by inappropriate use of the drug. In contrast, side-effects are defined as predictable, but distinct from the intended effects. They comprise unwanted, as well as positive or irrelevant effects of a drug appearing at normal dosage [1, 4].

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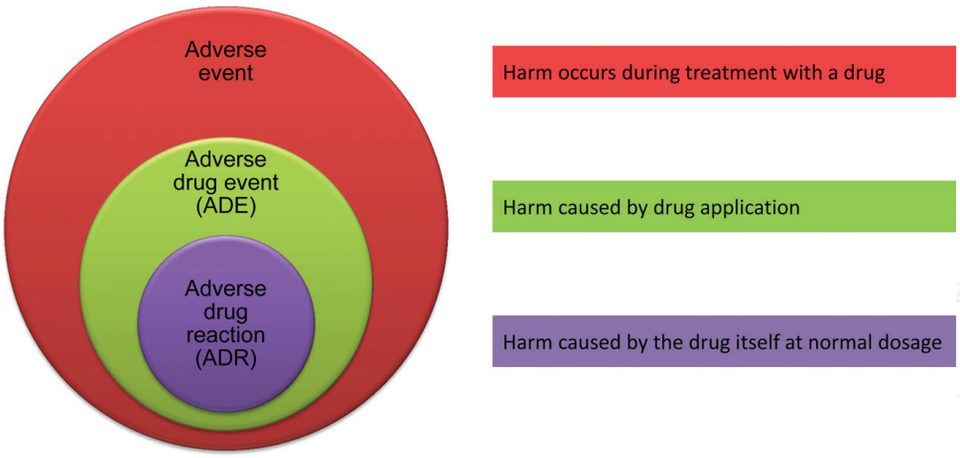

Figure 1. Classification of adverse events. Adverse events include all harmful events occurring during treatment with a drug without the necessity of a causal link between the drug and the reaction. If the use of medication is causal for the reaction, the condition is called adverse drug event. A subform of adverse drug events are adverse drug reactions that are triggered by the drug itself despite its appropriate dosage.

These noxious reactions to drugs are caused by distinct mechanisms, thus different forms of ADRs are distinguished as illustrated in **Figure 2**. Dose-dependent and predictable type A ADRs are explained by the pharmacological activity of the drug, whereas dose-independent type B reactions appear to be idiosyncratic [5].

With >80% the majority of all ADRs are classed among type A reactions that are rarely fatal [5, 6]. They are triggered by off-target binding to non-immune receptors, drug-drug interaction or toxicity; thus the clinical picture depends on the drug [7]. For example, nonsteroidal

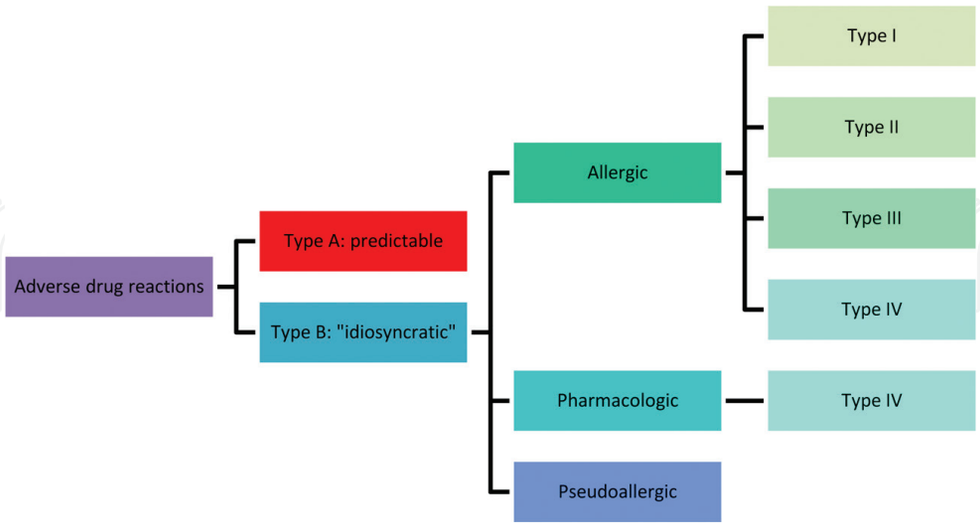

Figure 2. Classification of adverse drug reactions. The majority of all ADRs is dose-dependent and predictable type A reactions. Type B reactions occur less. The majority of all ADRs is dose-dependent and predictable type A reactions. Type B reactions occur less frequent and have a higher mortality. They are subdivided into allergic, pseudoallergic and pharmacologic reactions.

anti-inflammatory drugs (NSAIDs) are likely to cause gastrointestinal bleeding by inhibiting prostaglandin-synthesis, since prostaglandins do not only reduce inflammation, but also impede the production of protective mucus in the stomach. Another example are antihistamines of the first generation; being able to cross the blood-brain barrier the H1-receptor-antagonists also induce sedation by off-target binding.

Because these reactions to drugs are accounted for by their pharmacological mode of action, they are dose-dependent. Their emergence is comprehensible and predictable.

Type B ADRs are characterized by direct involvement of the immune system. They occur less frequently, but have an increased mortality rate [5, 7]. Type B reactions can affect almost every organ, but often feature involvement of the skin, liver and blood cells. The symptoms can be systemic as well as restricted to a single organ [8].

The main trigger of such drug hypersensitivity reactions are antibiotics, non-steroidal anti-inflammatory drugs and antiepileptics [9]. The nucleoside reverse transcriptase inhibitor abacavir utilized for treatment of human immunodeficiency virus type I patients leads to a severe and life-threatening hypersensitivity syndrome. Those affected individuals develop rashes, fever, gastrointestinal symptoms, lethargy, malaise, arthralgia, myalgia or respiratory symptoms in the first weeks after initiation of the intake of the drug. Abacavir hypersensitivity is highly associated with the human leukocyte antigen (HLA) allele HLA-B*57:01 [10, 11]. Another example of a type B adverse reaction is the allergy against penicillin. Symptoms include sudden anaphylaxis, hypotension, bronchospasm, angioedema and urticarial [12].

Drug hypersensitivity reactions often occur as skin exanthemas [9]. Several clinical pictures can be distinguished. Drug reaction with eosinophilia and systemic symptoms (DRESS) is known under various names including drug induced delayed multiple organ hypersensitivity syndrome (DHDMOHS), drug-induced hypersensitivity syndrome (DIHS), drug hypersensitivity syndrome (DHS) and hypersensitivity syndrome (HSS). It is characterized not only by cutaneous exanthema, but also by organ involvement, for example hepatitis, arthralgia and lymphadenopathy [13]. Danger signs indicating a DRESS are changes in blood count revealing eosinophilia or atypical lymphocytes and signs of organ involvement, namely high liver enzymes, high kidney values or lymphnode enlargement. At first, DRESS might resemble maculopapular exanthema, but in the course of the reaction it spreads over more than half the body [13]. Some drugs are highly suspected to induce DRESS: the antiepileptics carbamazepine, oxcarbazepine, lamotrigine phenytoin and phenobarbital, sulfonamides, as well as the uricostaticum allopurinol [13].

Other disease patterns are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In these conditions skin blisters and bullae rise, the skin detaches and erosions of mucous membrane are found [14]. The patients develop high fever, hypovolemia and complications with lung involvement are possible [15]. In SJS, the detachment of skin affects less than 10% of the body surface, whereas in TEN more than 30% of body surface detaches [16]. Approximately 48% of all TEN patients die due to the disease, for the elderly the mortality is 70%. SJS, SJS/TEN and TEN together have an overall mortality of 20–25% [15, 17]. In early stages tiny vesicles or crusts and painful or burning skin and mucosa

point towards SJS/TEN. Patients are positive for Nikolsky's sign, but specific laboratory parameters do not exist [18]. Medications with a high risk to induce SJS/TEN are the antiepileptics carbamazepine, lamotrigine, phenytoin, phenobarbital, some sulfonamides, the uricostaticum allopurinol, oxicam-NSAIDs, sulfasalazine and the antiretroviral drug nevirapine. The algorithm of drug causality for EN algorithm (ALDEN) helps to exclude or confirm the suspicion of SJS/TEN [19]. Currently, 67% of SJS/TEN-cases in Europe are drug induced with allopurinol being the main trigger [20].

Acute generalized exanthematous pustulosis (AGEP) has an acute onset with fever, large erythema and sterile, non-follicular pinhead-sized rapidly appearing pustules. Desquamation starts 4 to 10 days later. In AGEP neutrophilia also occurs; usually other internal organs are not, while the mucosa is little involved. Drugs associated with AGEP are for example aminopenicilins, quinolones and pristinamycine [21].

The first step for diagnosis of a drug hypersensitivity reaction is the analysis of the medical history of the patient [9]. Therefore, the symptomatology, the chronology of the symptoms, additional drug administration and the medical background are parameters to consider for a correct assessment [14]. A differential blood count is considered for confirmation of eosinophila in DRESS or neutrophilia in AGEP [9, 13, 22]. The involvement of other organs (liver, kidney, heart) is evaluated by investigation of laboratory parameters [13].

Skin tests and drug provocation tests enable in vivo identification of the drug responsible for the reactions. Patch tests are a safe method to identify the accountable drug in DRESS mediated by antiepileptics [9]. Nevertheless, patch, prick and intracutaneous skin tests are often insensitive, especially in case of non-immediate reactions to beta-lactam antibiotics as penicillin [23]. For drug provocation tests, only performed at specialist centers with resuscitative equipment, the administration of the suspected drug takes place under controlled conditions [24]. They are controversial, since severe reactions can be triggered [9, 24]. Likewise, provocation tests are not standardized for delayed reactions [9].

An advantage of in vitro tests is the safety of the patient who is not exposed to the drug. Additionally, they enable valuable insight into the pathomechanism of the drug allergy. However, in vitro tests are not standardized for all drugs and are not suitable to detect all types of drug hypersensitivity [9]. The lymphocyte transformation test (LTT) enables simultaneous testing of many drugs and drug concentrations [9]. Measurement of proliferation of drug-specific T-cells stimulated with the drug in question is enabled by incorporation of ^{3}H-thymidine [25]. The sensitivity of LTTs varies depending on the clinical manifestation and the drug, in AGEP and DRESS it is higher, as well as for beta-lactam antibiotics and antiepileptics. LTTs for SJS should be performed in the acute phase, whereas for DRESS the resolution phase has highest sensitivity. The number of cells releasing cytokines upon stimulation with the suspected drug can be determined by enzyme-linked immunosorbent spot assay (ELISpot) [25]. Upregulation of CD69 can be observed via flow cytometry, but this procedure is difficult to standardize [9]. When considering transitory peaks and degradation, cytokine synthesis and secretion can indicate hypersensitivity reactions. Measurement is possible via enzyme-linked immunosorbent assay, ELISpot and flow cytometry. Cytotoxicity can be determined equally [9]. Another test is

the basophil activation test (BAT) that can identify IgE-mediated reactions [26]. Combinations of these tests are currently best in order to diagnose a drug hypersensitivity reaction.

There are several approaches to divide drug hypersensitivity into classes depending on the time when first symptoms emerge, the type of immune mechanism or drug or the mode of drug action with immune cells [7]. The latter is composed of three groups (see **Figure 2**): Allergic reactions involve the innate and the adaptive immune system, pharmacologic reactions are exclusively triggered by T-cells, whereas pseudoallergic reactions are mediated by the innate immune system [7].

In detail, an allergic reaction to drugs is explained by the hapten/prohapten model where the drug itself or a reactive metabolite bind covalently to a high molecular weight protein. Thus, even small molecules that should not be recognized by the immune system become immunogenic [27–32]. The drug-carrier molecule can either activate the innate immune system via pattern recognition receptors or cells of the adaptive immune system react to the newly formed antigen after processing and presentation on HLA molecules [7]. Because of the hapten binding to multiple proteins, these allergic reactions are very heterogeneous [7, 29, 33]. A typical characteristic of allergic reactions is the immediate reaction of the patient due to the IgE-meditated urticaria, angioedema, rhinitis, bronchospasm and anaphylactic shock [34]. Drug allergies can also be triggered by IgG or T-cells [7]. Allergy against penicillin for example can manifest as IgE-mediated hypersensitivity reaction or as a delayed T-cell response [33, 35, 36].

Pseudoallergic type B reactions include mast cell and granulocyte activation, as well as involvement of enzymes and co-factors. Hence, the basis of those reactions is not a drug- or antigene-specific sensitization [7], but direct stimulation of effector cells [9]. NSAIDs do not only inhibit prostaglandin-synthesis, but also lead to increased amounts of leukotrienes that mediate inflammation. Therefore, the intake of NSAIDs can also result in asthma and rhinitis or angioedema [37].

Pharmacological reactions are characterized by noncovalent off-target binding of the drug or a metabolite to immune receptors. This excludes binding to the peptides presented by HLA molecules. Instead, the drug binds to either the T-cell receptor (TCR) or an HLA molecule, both are extremely polymorphic [7]. Abacavir hypersensitivity reactions belong to this category, since the drug binds to the peptide binding groove of HLA-B*57:01 [38].

2. The relevance of ADEs and ADRs

In consequence of the thalidomide disaster the world health organization (WHO) started the Program for International Drug Monitoring with the objective to improve the safety of medications [39]: In the early 60s of the last century the drug thalidomide that was sold under various names all over the world made history [40]. It was advertised as a sedative, tranquilizer and antiemetic without side-effects especially suited for pregnant women [41, 42]. By the end of 1960 first doubts emerged concerning toxic effects of the drug [43] but it was not until 1961

that its teratogenicity was stated [44–47]. Over time several adverse effects became apparent with peripheral neuropathy being the most frequent in patients taking thalidomide for long-term [48]. Also rashes and constipation turned out to be unexpected effects of the drug [40, 49].

When thalidomide was withdrawn in most countries in 1961–1962, more than 10,000 children with partially severe malformation had already been born [41, 42]. The number of serious cases was boosted by the demeanor of the manufacturer Grünenthal favoring the continued sale of the drug over informing the public of the toxic effects the company was aware of since 1959 [50]. This led to more consciousness about ADRs and other drug-related problems as for example medication errors or misuse/abuse of medicines and the raise of pharmacovigilance.

ADRs are an expensive burden on public health, they are under-diagnosed and under-reported [6, 51]. Already 30 years ago people began to wonder about unintended reactions to medication in hospitals. Initially, the question arose which method might be most successful in detecting such event [52]. The studies spotted remarkable observations: It was revealed that 86% of cases went unreported in Sweden [53], whereas in Canada under-reporting reached as much as 96% [54]. This might be due to the methods used to identify ADEs or due to unawareness of reporting systems [39]. There are different approaches to improve patient safety by early recognition and prevention of ADEs including voluntary reports and computer-based monitoring. Traditional detection methods as voluntary reporting are inconvenient and have the disadvantage of relying on the commitment of physicians and nurses [55]. Already in 1991 Classen, Pestotnik [55] reported that their computerized surveillance of ADEs drastically elevated their detection and reporting. Based on information about abrupt discontinuation of drugs, antidote ordering and anomalous laboratory values, the computer program recognized 641 of 731 ADEs in 36,653 patients, whereas only 9 of those ADEs were revealed by the traditional detection methods [55]. This result is coincident with other publications reporting that physicians only identified a third of ADRs notified by automatic signals generated from laboratory signals [56] and that half of true-positive alerts were unrecognized prior to the warning [57].

Evans, Pestotnik [58] stated that the type and the intensity of an ADE had implications on the length and costs of the stay in hospital. While patients without ADEs stayed for an average of 5 days, patients experiencing a type A or type B reaction had prolonged stays of 14 or 17 days, respectively. Hence, the costs of hospitalization increased by 3.7- or 4.8-fold for these patients. Moderate ADEs led to extended stays of 13 days and a 3.6-fold increase in costs; severe ADEs prolonged the stay to an average of 20 days and caused a 6-fold increase in costs.

Different studies considered 30–50% of all ADEs [2, 59] to be preventable, whereas others appraised 50–80% of all ADRs to be avoidable [6, 51, 56, 60, 61]. Interestingly, severe reactions were more frequently classified as preventable than mild reactions [2, 59]. Nevertheless, about 3% of all deaths and approximately 6.4% of hospital-fatalities in the UK are caused by ADRs [62]. There are several reasons for those preventable ADEs to happen. Too high doses of drugs in relation to the patient's age, renal function, weight and underlying disease were identified by Evans, Pestotnik [58] as a main reason for the moderate reactions. Errors during ordering and administration were found causal for most ADEs by Bates, Cullen [59]; other

studies claimed ADEs to emerge more likely due to errors while ordering and monitoring, whereas dispensing and administration of the drugs rarely caused the reactions [2].

As a possible strategy to improve patient safety, several authors have demonstrated significant prevention of ADEs by the application of pharmacy alerts for known drug allergies [57, 58], as well as presence of pharmacists on ward rounds, improved monitoring and education of prescribing [6, 63].

3. Mechanisms of type B ADRs

Most drugs are not antigenic due to their small size (<1000 Da), however, by forming a hapten or prohapten through covalent binding to carrier proteins the drug-protein complex becomes chemically reactive and can subsequently trigger an immune response. Prohaptens are precursor haptens that become reactive by metabolizing the drug to generate active haptens. In order to cause an allergic reaction, these hapten complexes have to be processed by antigen presenting cells (APC). After migration to the local lymphoid tissue, sensitization of naïve T-cells or stimulation of B cells can occur. Primed T-cells proliferate and act as effector T-cells and may also aide the differentiation of B cells to plasma cells that produce drug-hapten specific IgE or IgG antibodies, depending on the presence of either Th1 or Th2 helper cells. Accordingly, allergic hypersensitivity reactions are categorized into four types (Type I–IV) based on the classification system established by Gell & Coombs [7].

4. Antibody mediated hypersensitivity reactions (Type I–III)

Type I–III reactions (**Figure 3**) occur if drug-specific B cells differentiate into antibody producing plasma cells through $CD4^+$ Th2 cell stimulation. In the case of Type I reactions these plasma cells produce IgE antibodies. Many of these reactions are caused by antibiotics of the β-lactam family (e.g. penicillin and its derivatives) that can lead to symptoms ranging from mild skin reaction to the life threatening anaphylactic shock. In the case of penicillin, the antibiotic binds covalently to high-molecular weight proteins such as albumin [64] thus forming a molecule complex that can be recognized by IgE antibodies. During sensitization, these IgE antibodies bind to mast cells in tissues and basophiles in the blood *via* the FcεRI receptor. Subsequent cross-linking of the IgE antibody with the antigen elicits the type I reaction resulting in the release of histamines, leukotrienes and serotonin as well as prostaglandin causing allergic symptoms [14]. Type I reactions are immediate reactions that take place directly after administration of the drug or up to 2 hours later. Typically, clinical manifestations contain symptoms such as urticaria, mild skin rashes and anaphylactic shock.

In non-immediate type II and type III reactions symptoms emerge 5 to 21 days after administration of the drug [14], however, first symptoms are usually observed after 24 to 48 hours. Both types are primarily IgG-mediated. Damage mediated by tissue-specific IgG or IgM antibodies is the basis for type II reactions: On exposure, the drug forms a hapten with a

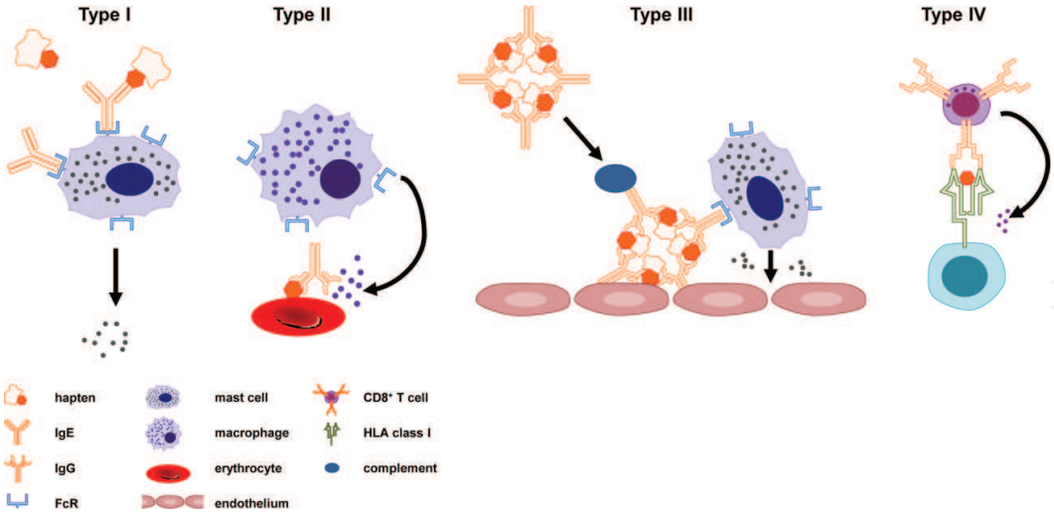

Figure 3. Type I – IV drug-related hypersensitivity reactions.

self-protein thus creating a modified self-protein. Binding of IgG or IgM to the modified self-tissue is followed by activation of normal immunoglobulin effectors. Drug specific type II reactions are mostly associated with the destruction of red blood cells and platelets, where the respective drug bound to the cell surface serves as an antigenic target for IgG antibodies leading to antibody-dependent cell-mediated cytotoxicity (ADCC). Consequently, the cell bound antibody then triggers clearance of the cell from the circulation by macrophages or NK cells that recognize the Fc part of the IgG antibodies *via* the FcγRIII (CD16) surface receptor. Examples are hemolytic anemia as an adverse reaction to methyldopa or leukopenia in the case of aminopyrine.

Type III hypersensitivity reactions are caused by soluble drug-haptens that form immune complexes with IgG antibodies [14]. Larger aggregates are fixed by complement und consecutively cleared by phagocytes, however, smaller immune complexes deposit at local tissue sites where FcR binding on leukocytes and mast cells induces an inflammatory response leading to increased vascular permeability. Conditions that arise from type III reactions are serum sickness (especially β-lactams), drug-induced lupus erythematosus and thrombocytopenia (quinidine) or vasculitis or even DRESS (minocycline).

5. T-cell-mediated drug hypersensitivity (type IV) without prior drug exposure

Type IV reactions (**Figure 3**) take the longest time to develop, ranging from 2 days up to 20 days until first symptoms emerge. Symptoms include mild conditions such as MPE to more severe conditions such as TEN or SJS. Type IV ADRs are T-cell mediated drug hypersensitivity reactions based on the erroneous T-cell activation through HLA molecules on the surface of endogenous cells. Different modes of activation can be distinguished, whether the antigen is formed by binding of the drug to a self-protein, thus creating a foreign antigen for T-cell recognition

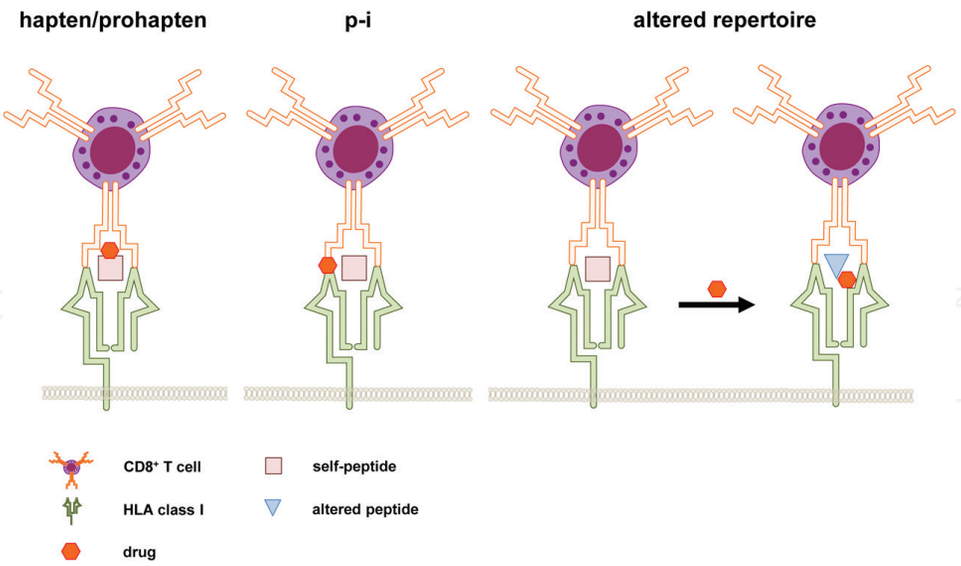

Figure 4. Overview of the models explaining T cell-mediated hypersensitivity.

(allergic), or the drug interfering directly or indirectly with the interaction between T-cell receptor (TCR) and HLA (pharmacological). The processing and interference of presentation by APCs leads to an immunostimulatory potential that manifests in delayed hypersensitivity reactions [65] and although direct recognition of the drug as an immunogen is more common with non-human protein therapeutics [66], most small molecules are not direct immunogens. Their potential for eliciting a hypersensitivity reaction is explained by either of the following models (**Figure 4**): Hapten model, p-i model and altered peptide repertoire model [7].

6. The hapten/prohapten model

The hapten model is based on the binding of small chemicals to proteins or peptides and thus generating new antigenic determinants. These complexes are processed by APCs in lymphoid tissues and generate antigenic hapten-peptides that have the ability to stimulate T-cells in an HLA dependent manner. Examples are sensitive reactions to β-lactam antibiotics. Penicillin, for instance, is known to bind extracellular proteins, in particular to lysine residues of serum albumin [67]. In the case of penicillin, haptenated peptides are presented to $CD4^+$ T-cells by HLA-DRB1 [68]. Chemically inert drugs may also produce delayed hypersensitivity reactions if the metabolite of the otherwise non-reactive drug becomes active. An example here is sulfamethoxazole. In the liver CYP2C9 modifies sulfamethoxazole into hydroxylamine metabolite that is reactive, converts spontaneously to nitroso sulfamethoxazole that readily binds protein cysteine residues of extracellular and cellular proteins [69].

7. The p-i model

After it became apparent that the hapten model is not sufficient to explain the diversity of different hypersensitivity reactions, the pharmacological interaction with immune receptors

(p-i) model and the altered peptide repertoire model were proposed. The p-i model postulates that binding of the drug itself to either the TCR or the HLA molecule may elicit the hypersensitivity reaction [70]. Such binding is independent from metabolites and processing by APCs and additionally, the binding is non-covalent and therefore potentially weak [71]. This means the p-i mechanism is reversible and binding can occur at the interaction sites of the TCR-HLA complex as well as outside of the binding regions. In either case, the drug-binding interferes with the interaction between the HLA molecule and the TCR. In general, as part of the p-i concept, the drug binding has to induce functional changes and the mechanism is immediate because it directly interferes with the already present system. Also, the innate immune system and B cells are not involved because antigen processing is not involved in the p-i concept. Because these structures are allele specific and therefore specific to highly polymorphic regions, this immune response is only observed for carriers of certain HLA alleles. Additionally, the drug can bind in the groove and change the features of the pockets in the peptide binding groove, so that even though a correct peptide is presented the change in overall conformity can lead to T-cell activation. Examples for the p-i concept are the interaction of allopurinol with HLA-B*58:01 where binding of the drug leads to immediate T-cell activation that was not limited to a specific TCR Vβ pattern [72].

8. The altered peptide repertoire model

The relation between delayed hypersensitivity reactions and HLA associations is further explained by the altered peptide repertoire model. This concept is based on the binding of the drug inside the peptide binding groove during HLA assembly in the ER [38]. However, binding in the peptide binding groove leads to altered peptide specificity and thus changes the presented self-repertoire. Consequently, an erroneous T-cell response is triggered because the TCR does not recognize these altered peptides as self anymore. This model was first based on findings that were made from the peptide elution studies and crystal structure of HLA-B*57:01 with abacavir [38, 73]. The structure demonstrated that Abacavir resides within the C, D, E and F pocket of the peptide binding groove influencing the peptide binding capacity of HLA-B*57:01 leading to a shift in the presented repertoire. For endogenous T-cells, this poses an allogenic antigen prompting an immune response similar to the mechanism of allograft rejection and graft versus host disease (GvHD).

9. HLA-mediated ADRs

Through genome-wide association studies an increasing number of associations between certain allelic HLA variants and drug-hypersensitivities could be identified [74]. In order to secure safer treatment of patients, it is essential to understand the underlying mechanisms [75]. The discovery of an association between ADRs and certain HLA alleles represented an important medical step towards the prediction and prophylaxis of Type B ADRs. These particular HLA-mediated hypersensitivity reactions are highly specific; hence HLA subtypes that are linked to ADRs represent biomarkers for the determination of individual medications. HLA molecules bind and present peptides of the intracellular proteomic content; their origin

is determined by the health status of the cell. During pathological conditions, HLA molecules can bind peptides of non-self origin and display targets for effector cells that scan peptide-HLA complexes on the cellular surface for self- / non-self discrimination. The HLA-system is extremely polymorphic. For most HLA genes several allelic variants exist, most of them are distinguished by amino acid (AA) exchanges within the peptide binding region (PBR). Structural alterations within the PBR result in the selection and binding of peptides exhibiting differential features (origin, sequence, length). Every single peptide alters the accessible surface of a given peptide-HLA complex for recognition by an effector cell receptor. T-cell responses can be triggered through the recognition of single AA mismatches that alter the biophysical state of the PBR and thus the features of the bound peptides, the heavy chain and hence the mode of peptide loading and/or the half life time of the pHLA complexes.

The first discovered and most prominent example is the association between the antiretroviral drug abacavir and HLA B*57:01 [10]. Abacavir is a nucleoside analogue of guanosine, it inhibits competitively the reverse transcriptase of the retrovirus HIV. 5–8% of treated patients develop hypersensitivity reactions, comprising fever, fatigue, gastrointestinal symptoms up to life threatening, multiorgan diseases. HLA-restricted hypersensitivity reactions triggered by abacavir are verified to be $CD8^+$ T-cell-mediated [76], using a broad repertoire of TCR clonotypes [75, 77]. Thereby, Abacavir-induced $CD8^+$ T-cell activation is elicited by an altered repertoire of self-peptides, presented by HLA B*57:01 [78]. Due to the high incidence of HLA B*57:01, all patients are typed for HLA class I molecules prior to therapy in order to protect patients from hypersensitivity syndrome and the pharmaceutical industry from its associated costs [79, 80].

Another example is the HLA-associated ADR induced by Allopurinol. This inhibitor of xanthine oxidase, applied in gout and hyperuricemia, causes severe cutaneous adverse reactions in patients carrying the HLA B*58:01 gene [81].

CBZ-induced ADRs are strongly associated with two HLA genotypes, HLA B*15:02 in Han Chinese [82, 83] and HLA A*31:01 in Caucasian and Japanese population [84, 85]. Both HLA alleles differ substantially in their AA composition and their immune function. However, a strong discrimination between the clinical outcome of HLA-B*15:02 or A*31:01 positive patients following CBZ administration can be observed. The anticonvulsive drug CBZ is commonly used to treat epilepsy, trigeminal neuralgia, bipolar disorder or chronic pain. In 5% of cases, therapy with CBZ is discontinued because of adverse drug reactions. Nevertheless, CBZ is commonly applied due to its therapeutic success and its comparable tolerability. CBZ-induced ADRs vary in their severity from mild maculopapular exanthema (MPE) or hypersensitivity syndrome (HSS) to life-threatening Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [86, 87]. The ADR-causing mechanism, triggered by CBZ, is not yet completely discovered. SJS and TEN are caused by cytotoxic $CD8^+$ T-cells [88], MPE and HSS also involve skin-infiltrating $CD4^+$ T-cells. These $CD4^+$ T-cells damage the skin by secreting inter alia perforin and granzyme B [89]. Interestingly, HLA B*15:02 is associated with SJS/TEN, but not with MPE or HSS [86]. In contrast, HLA A*31:01 is associated with HSS, MPE and SJS/TEN [90]. Associations are detected in Japanese, Han Chinese as well as in European ancestry [84–86]. The prevalence of this allele is 2–5% in Northern European population, 2% in Han Chinese population and 9% in Japanese population [84]. According to the broad range

of HLA A*31:01-restricted CBZ-induces ADRs, different types of CBZ-specific T-cells were isolated of patient's peripheral blood: $CD3^+/CD4^+$, $CD3^+/CD8^+$ as well as $CD3^+/CD4^+/CD8^+$ T-cells [91, 92].

Thereby, further association between CBZ-specific $CD4^+$ T-cell response and the HLA class II molecules HLA DR and DP could be detected. Especially, HLA-DRB1*04:04 seems to be associated with CBZ-induced ADR driven by $CD4^+$ T-cells. This HLA allele occurs commonly in a haplotype block with HLA A*31:01 in Caucasians [92, 93]. While HLA A*31:01-restricted CBZ-induced ADRs are widely unexplained [90], there are several suggestions about the mechanism of HLA B*15:02-restricted CBZ-induced ADRs. STS/TEN are triggered by cytotoxic T-cells inter alia via perforins, granzyme B and granulysin [94]. There are reasonable presumptions, that T-cell activation occurs via direct interaction of CBZ with the immunoreceptor [95], in accordance with the p-i model [96, 75]. Confirmed T-cell activation independently of metabolism of CBZ and intracellular antigen processing, supports this hypothesis [97, 95]. In contrast, presentation of an altered self-peptide repertoire by HLA-B*15:02 due to CBZ-exposure is reported, leading to the presumption, the T-cell receptor is activated according to altered repertoire model [38]. Additionally, the presence of HLA B*15:02 is not a sufficient characteristic to elicit $CD8^+$ T-cell response, since not all carriers are responders [35, 98]. However, restricted usage of TCR clonotype is required for immune activation [99]. Thus, it could be illustrated that only HLA B*15:02-typed patients with T-cells, expressing the TCR Vβ 11-ISGSY, react hypersensitive to CBZ [100].

The mechanism of HLA-meditated hypersensitivity reactions to drugs are not completely understood, yet. Polymorphic residues within a given HLA molecule affect their conformation and their bound peptides. Open questions remain i) how does the drug interact with selected residues of the HLA-molecules heavy chain?, ii) is the reaction triggered by the drug itself or by a metabolite?, iii) can non-responders to a drug be attributed to the presence or a lack of given TCRs and their immunological vitality?

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