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Mini Review

A Brief Review of the Mechanisms of Drug Hypersensitivity

Zamir Calamita[1]* and Larissa Barbosa Lopes[2]

[1]*Medical Immunologist, PhD, Head of the Discipline of Allergy and Immunopathology of the Marília Medical School (Faculdade de Medicina de Marília), Marília, São Paulo, Brazil*

[2]*Biomedical, PhD, Volunteer Researcher, Discipline of Hematology and Hemotherapy, Federal University of São Paulo (UNIFESP), São Paulo, Brazil*

***Corresponding Author:** Zamir Calamita, Medical Immunologist, PhD, Head of the Discipline of Allergy and Immunopathology of the Marília Medical School (Faculdade de Medicina de Marília), Marília, São Paulo, Brazil

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Abstract

Adverse drug reactions when occurring unexpectedly, within recommended dosages and routes, are called hypersensitivity reactions. They may be due to immunological or non-immunological mechanisms. When immune mechanisms are involved they are called allergic reactions. The drug hypersensitivity reactions are historically grouped according to the well-established classification of Gell and Coombs; however, more recent studies have been able to incorporate new knowledge into the already existing traditional model, enabling a better understanding of these reactions. The review of the various pathophysiological mechanisms involved in the drug hypersensitivity response is fundamental for an adequate diagnostic investigation and clinical driving in these cases. This article will allow the reader to review, in a succinct and updated way, this subject, which is of great relevance in the health field.

Keywords: Adverse Drug Reaction; Drug Allergy; Drug Hypersensitivity

Introduction

Drug hypersensitivity reactions (DHRs) are found in more than 7.0% of the general population [1,2]. Adverse drug reaction (ADR), according to the World Health Organization is defined as "any non-therapeutic effect at the doses usually employed for the prevention, diagnosis or treatment of diseases" [3-5]. They can be classified as predictable (common), also denominated type A and can occur in any individual, or unpredictable (unusual), also denominated type B [6]. As an example of adverse reactions of type A, we could mention the side effects of the medications such as drowsiness and dry mouth, secondary to the use of the tricyclic antidepressants, or abdominal discomfort that can occur with the use of various types of medications. On the other hand, type B reactions are associated with individual susceptibility and are exemplified by the idiosyncratic reactions and the DHRs. The term "allergy" is the most recognized by the general population and there has been a tendency in recent decades to use the word "allergy" to describe all kinds of unexpected reactions in the skin and mucosal surfaces, arising from a given stimulation, in general by drug or food. According to the World Allergy Organization (WAO), also supported by a Task Force of the European Academy of Allergy and Clinical Immunology (EAAIC), the term hypersensitivity, in general, is defined as "the situation in which objectively reproducible signs or symptoms occur, initiated by a defined stimulus set at a normally tolerated dose" [7], In the case of drug use, the DHRs are those that occur unexpectedly due to the use of drugs within the recommended dosages and routes. They may be of an allergic cause, when immunological mechanisms are involved, or non-allergic, when triggered by non-immunological mechanisms. The DHRs correspond to about 15 to 25% of all ADRs [4,6], which demonstrates the need for their better understanding and the importance of the subject.

This is a min-review of the literature, whose objective is to inform the reader, in a succinct and updated way, the main mechanisms involved in the reactions of DHRs.

Mechanisms involved in the DHRs

Historically, the DHRs are didactically described according to the classification of Gell and Coombs, although most of them do not involve immunological mechanisms due to the fact that the drugs are generally small in molecular weight and are therefore not considered immunogenic (complete antigens themselves) [5,8]. Consequently, they would need to act as haptens to trigger an immune response. Thus, didactically, the DHRs are firstly divided into two main groups: the allergic DHRs in which immunological mechanisms are involved, and non-allergic DHRs, formerly called pseudoallergic [5], in which other (non-immunological) mechanisms are involved [4-6,9]. Among the several possible mechanisms involved in the pathophysiology of non-allergic DHRs the following are worth mentioning: a) non-specific direct stimulus (independent of specific IgE binding) of degranulation of basophils and mast cells (e.g. morphine and codeine) with the release of vasoactive mediators; b) accumulation of bradykinin (angiotensin-converting enzyme inhibitors, iodinated contrast); c) activation of the complement (protamine, iodinated contrast); d) osmolarity difference with stimulation of mast cell and basophils degranulation (iodinated contrast); and e) pharmacological action in the metabolism of arachidonic acid (ASA and other nonsteroidal anti-inflammatory drugs) [10]. Regarding the media of iodinated contrast, some researchers believe that, in a small percentage, the hypersensitivity reactions also occur through the immunological IgE-mediated mechanism [9]. As for non-steroidal anti-inflammatory drugs (NSAIDs), the possibility of a specific IgE-mediated reaction to a given anti-inflammatory would also be possible; however, in the vast majority of cases, the reaction is to the general group of NSAIDs, and is believed to be due to the preferential inhibition of the cyclooxygenase-1 enzyme, with a consequent decrease in the production of prostaglandin E2 and subsequent higher activation of 5-lipoxygenase, leading to a higher production of leukotrienes, and consequently to clinical manifestations of hypersensitivity (e.g. urticaria, angioedema , bronchospasm) [10]. In allergic DHRs where immunological mechanisms are involved, it is interesting to initially comment on some basic concepts: the T lymphocyte response is stimulated when the antigen-presenting cells (APCs) have on their surface MHC molecules loaded with peptides for which the lymphocytes have specific receptors (TCRs). The clonal proliferation of T lymphocytes occurs in the presence of co-stimulation molecules. Class I MHC molecules present peptides of intracellular origin with 8-10 amino acids to CD8+ T lymphocytes, and MHC class II molecules present peptides of extracellular origin with 12-16 amino acids to CD4+ T lymphocytes. The cytokines produced by APCs and other cytokines existing in the microenvironment, in which APC-T lymphocyte interaction occurs, determine the polarization of lymphocytes (Th1, Th2, Th17, Treg, etc.) and consequently the predominant type of immune response [11]. The interaction between activated CD4+ T lymphocytes and B lymphocytes induces the clonal proliferation of B lymphocytes and the production of specific antibodies. The recognition of large molecules obeys the usual principles of antigenicity/immunogenicity; however, most drugs are small molecules, with some drugs having lower molecular weights than simple amino acids (amino acids have molecular weights between 75 Da for Glycine and 204 Da for Tryptophan); as an example, penicillin is slightly larger than tryptophan, whereas allopurinol is smaller than a few amino acids [11]. Considering that MHC class I molecules present peptides with 8 to 10 amino acids (~ 900-1100 Da) to the TCR/CD8+ and that MHC class II presents peptides with 12 to 16 amino acids (~ 1300-1800 Da) to the TCR/CD4+, the way these small molecules are recognized by the receptors of the immune system is not obvious and has been the subject of scientific curiosity for decades, generating several models to explain the recognition of small drugs by specific receptors of lymphocytes, such as haptenization theories, and the p-i concept [11-14]. Another aspect worth emphasizing is the fact that DHRs may not occur to the drug itself (in natura), but to some metabolites of the drug. Then, the drug or its metabolite would function as a hapten attaching itself to some protein in the plasma or cell (generating a "neoantigen") and then becoming immunogenic to the body. Pichler [12-14] proposed a new model of specific recognition that he called "p-i concept" (pharmacological interaction of drugs with immune receptors). According to the p-i model, the drugs do not function as antigens, but cause hypersensitivity reactions by binding directly to the TCR or HLA, forming a non-covalent binding to the immune receptor, by intermolecular forces (van der Waals, electrostatic or hydrogen bonds), inducing the activation and clonal proliferation of T lymphocytes after contact with APC. Lymphocyte receptors (in the individual) as well as HLA molecules (in the population) are highly variable in their conformation and in antigen binding sites (more than 1011 different TCRs may occur in an individual and more than 9900 HLA class I alleles and over 3000 class II are described in the human population - http://www.allelefrequencies.net/default.asp) [11]. According to the p-i model, some hypersensitivity reactions are predictable and strongly associated with alleles or HLA haplotypes, and stimulation of T lymphocyte clones may occur either by the drug binding directly to the TCR (p-iTCR) or by binding of the drug to HLA (p-iHLA). Didactically, the

authors classified the DHRs, according to the well-known hypersensitivity classification of Gell and Coombs, into four major groups (Type I, II, III and IV), and type IV DHR was further subdivided into four other subtypes [6,11-15]. Type I hypersensitivity, also called "immediate", occurs after the binding of the antigen generally haptenized to IgE class specific antibodies located on the surface of mast cells and basophils, inducing the degranulation of preformed mediators (histamine, tryptase, etc.) and neoformed (leukotrienes, TNF-α, etc.), resulting in several clinical manifestations such as bronchospasm, urticaria, angioedema, anaphylaxis, etc., usually within the first hour after exposure, in which case, theoretically there would be a need for prior contact with the drug (e.g. penicillins and other antibiotics, NSAIDs, etc.), in order to have prior sensitization. Hypersensitivity reactions type II and III are usually late reactions, usually occurring within one to two weeks after the start of some drug use, and in both cases, they are related to IgG and IgM class antibodies. In the type II reaction (also called cytotoxic), DHRs occur on the surface of the cells through specific IgG or IgM antibodies directed at drug-hapten coated cells that, in this way, become "targets" of others cells with cytotoxic capacity (such as NK lymphocytes), phagocytic cells (in particular the mononuclear phagocytic system). Also, the cell lysis happens by complement fixation and formation of the membrane attack complex. Exemplifying, when some drugs (e.g. penicillins and other antibiotics, methyldopa, quinidine, NSAIDs, etc.) bind to molecules on the surface of erythrocytes or platelets, they may trigger an immune reaction, since these cells are structurally modified by binding to the drug (hapten) becoming “targets” for anti-drug IgG or IgM antibodies that will lead to destruction of the cell, causing hemolytic anemia or thrombocytopenia. In the case of type III DHRs, also known as hypersensitivity by immunocomplexes, it occurs when a particular drug (e.g. antibiotics, NSAIDs, monoclonal antibodies, etc.) triggers the formation of circulating soluble immunocomplexes (antigen-antibody) that, when deposited in the vascular endothelium of some tissues, activate the complement cascade causing vessel inflammation (vasculitis) and consequently damage the organs involved. Type IV DHRs, also referred to as late, delayed, or cellular, include responses mediated by various types of T lymphocytes, usually occurring after several days of exposure (up to one month), but may be rapid, in a few hours, if p-i is involved. Several drugs may be implicated in triggering such reactions (anti-infectives, anticonvulsants, etc.) and often reach the skin (an organ rich in T lymphocytes and APCs) and can lead to severe and fatal symptomatology. According to the type of cytokines produced by the T lymphocytes and with the type of effector cells, type IV reactions are divided into four subtypes: Type IVa - mediated by Th1 cells producing IFN-γ and TNF-α, with predominantly monocyte/macrophage activation, occurring in eczema; Type IVb - mediated by Th2 cells producing IL4/IL5/IL13 with recruitment and activation of eosinophils, which may cause serious reactions, such as the drug reaction with eosinophilia and systemic symptoms (DRESS), and are often associated with the chronic phase of type I DHR; Type IVc - mediated by CD4+ and CD8+ T lymphocytes with cytotoxic capacity, may cause mild reactions such as maculopapular rash, or severe reactions with extensive tissue destruction such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or toxic hepatitis; in this type of DHR the T lymphocytes themselves are the effector cells, through the expression of FasL and the production of granzymes, perforin, and granulysin (a molecule produced by CD8+ and NK T lymphocytes and recently identified as mainly responsible for the generalized death of keratinocytes in SJS or TEN); Type IVd - mediated by lymphocytes producing IL-8 with neutrophil recruitment leading to sterile pustular reactions such as acute generalized exanthematous pustulosis (AGEP). Hypersensitivity reactions to type I and IV drugs are more frequent than types II or III. The classification of drug hypersensitivity reactions is briefly presented in Figure 1 and Table 1.

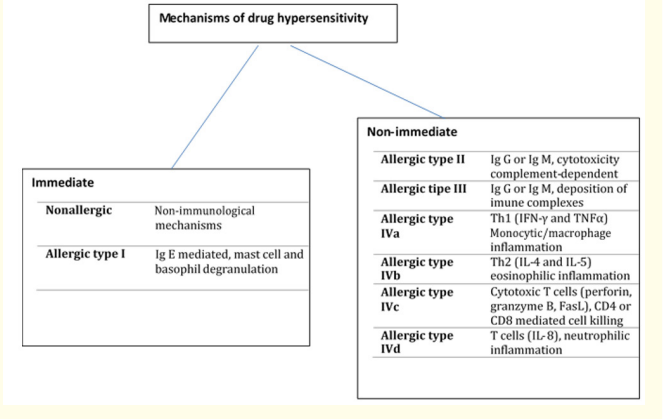

Figure 1: Schematic diagram of mechanisms of drug hypersensitivity.

Conclusion

This review made it possible to present to the readers a brief update on the main pathophysiological mechanisms involved in

Type of drug hypersensitivity reaction	Pathophysiology	Clinical presentation	Probable chronology of the reaction
Nonallergic	Non-immunological mechanisms	Anaphylaxis, urticaria angioedema, bronchospasm	Immediate
Allergic type I	Ig E mediated, mast cell and basophil degranulation	Anaphylaxis, urticaria angioedema, bronchospasm	Immediate
Allergic type II	Ig G or Ig M, cytotoxicity complement-dependent	Blood cell dyscrasia (Cytopenia)	Non-immediate
Allergic tipe III	Ig G or Ig M, deposition of imune complexes	Vasculitis	Non-immediate
Allergic type IVa	Th1 (IFN-γ and TNFα) Monocytic/macrophage inflammation	Eczema	Non-immediate
Allergic type IVb	Th2 (IL-4 and IL-5) eosinophilic inflammation	Maculopapular exanthema, DRESS[1]	Non-immediate
Allergic type IVc	Cytotoxic T cells (perforin, granzyme B, FasL), CD4 or CD8 mediated cell killing	Maculopapular exanthema, SJS[2]/TEN[3], bullous exanthema	Non-immediate
Allergic type IVd	T cells (IL-8), neutrophilic inflammation	Pustular exanthema	Non-immediate

Table 1. Classification of drug hypersensitivities (adapted from [6,10-12,14]).

[1]Drug Rash with Eosinophilia and Systemic Symptoms, [2]Stevens-Johnson syndrome, [3]Toxic epidermal necrolysis.

DHRs, thus allowing a better understanding of the clinical manifestations in such cases. It is noticed that new knowledge was introduced to the classic concept based on the classification of Gell and Coombs, allowing a better understanding of the physiopathology of DHR.

Conflict of Interest Statement

No conflict of interest.

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