Review

DOI: 10.5582/ddt.2011.v5.5.211

Agents that induce pseudo-allergic reaction

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ABSTRACT: Pseudo-allergic reactions may result from the activation of inflammatory or anaphylactic mechanisms independent of antigen-specific immune responses. Recent statistics show that pseudo-allergic reactions may represent as high as two thirds of all immediate hypersensitivity reactions, implying a great amount of morbidity and numerous health care costs. In this review, we concentrate on agents mediating pseudo-allergic reactions and evaluate accurately the available information on their modes of action. The agents discussed here are divided into three types: (*i*) Direct mast cell activators, which may activate mast cells in an IgE-independent manner, such as opioid drugs, basic secretagogues and calcium ionophore A23187; (*ii*) Complement activators, including liposomes, radiocontrast media and Cremophor EL, which may activate the complement system by different pathways: the classical pathway, the mannose-binding lectin pathway or the alternative pathway; (*iii*) Nonsteroidal anti-inflammatory drugs, which may inhibit the function of cyclooxygenase-1, resulting in the occurrence of adverse reactions. In addition, nonclinical detection methods of pseudo-allergic reactions are also reviewed in order to supply valuable information for clinical diagnosis.

Keywords: Pseudo-allergic reaction, anaphylaxis, mast cell, complement, nonsteroidal anti-inflammatory drugs

1. Introduction

Hypersensitivity reactions have been classified into four types from I to IV by Coombs and Gell in 1963 (*1*). With further studies of adverse drug reactions, a new type of hypersensitivity reaction has increasingly been recognized (*2*), which is an acute, potentially fatal, systemic hypersensitivity reaction arising *via* a non-IgE-dependent mechanism. The reaction occurs at the first contact with the drug without prior sensitization, and does not increase upon repeated exposure. Because of its similarity to a type I allergy in clinical symptoms (Table 1), it has long been termed a pseudo-allergic reaction. In 2001, the European Academy of Allergology and Clinical Immunology (EAACI) proposed to use the term "nonallergic anaphylaxis" instead of "pseudo-allergic reaction" when immunologic mechanisms cannot be proven (*3,4*). However, the reactions discussed here have several causes, including but not limited to complement activation, which belong to antigen-independent immune responses. In addition, the term "pseudo-allergic reaction" was still used in the paper "Guidance for Industry: Immunotoxicology evaluation of investigational new drugs" published by FDA in 2002 (*5*). Therefore, we use the term "pseudo-allergic reaction" here.

Pseudo-allergic reactions can be attributed to the activation of inflammatory or anaphylactic mechanisms unrelated to antigen-specific immune responses (*5*). These reactions may be induced by the following agents: direct mast cell activators, complement activators and nonsteroidal anti-inflammatory drugs. A series of physiological and pathological reactions can be induced by these agents in human bodies resulting in the appearance of symptoms of pseudo-allergic reactions such as nausea, dermatitis, hypotension, anaphylactic shock and even death (Table 1).

It has been indicated that more than 30% of adverse drug reactions are immediate hypersensitivity reactions (*6*), and as high as two thirds of all immediate hypersensitivity reactions may be pseudo-allergic reactions (*7*), implying a great deal of morbidity and numerous health care costs every year (*8*). Owing to the lack of systematic study of the pathogenesis of these reactions, and the dearth of universal agreement on their diagnostic criteria, the epidemiology, pathophysiology, and management of these reactions are greatly inhibited, resulting in a failure to diagnose and treat pseudo-allergic reactions in a consistent manner (*9*). Therefore, the aim of this review is to introduce the possible causes of pseudo-allergic reactions, based on agents of known structures that are capable of mediating the reactions. Nonclinical detection methods of pseudo-allergic reactions are also reviewed and discussed.

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Table 1. Symptoms of pseudo-allergic reactions

System	Potential symptoms and signs
Respiratory	Sneezing, coughing, asthma attack, bronchospasm, choking, rhinitis, tachypnea, stridor
Gastrointestinal	Vomiting, nausea, abdominal pain, diarrhea
Cardiovascular	Angioedema, hypertension, angina pectoris, ventricular tachycardia, arrhythmias, cardiac arrest
Neuromuscular	Chills, confusion, muscle pain
Skin and mucosa	Rash, cyanosis, dermatitis, erythema, pruritus, skin eruptions, urticaria, conjunctivitis
Severe adverse reactions	Anaphylactic shock, death

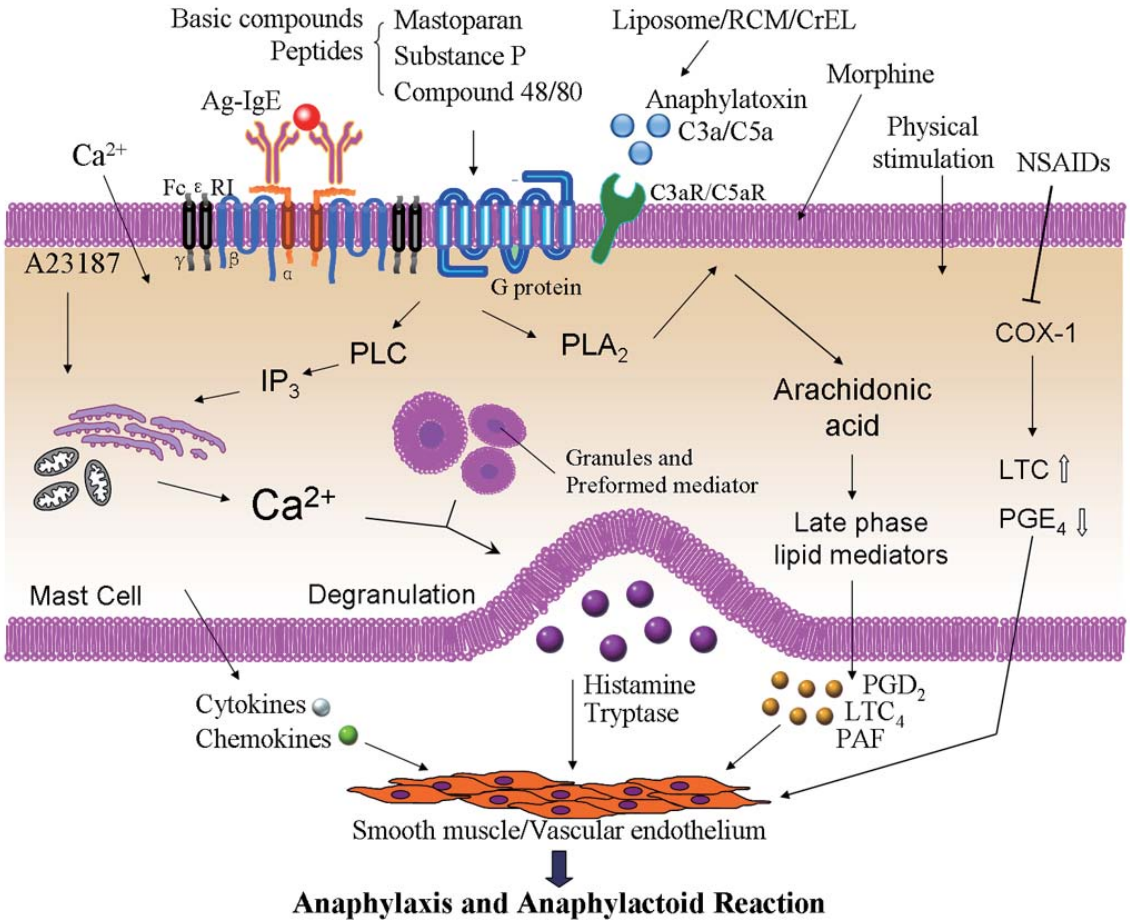

Figure 1. Pathways and mediators of anaphylaxis and pseudo-allergic reaction. Mast cells play a significant role in allergic and pseudo-allergic reactions. Activation of mast cells can be mediated both in an IgE dependent and independent manner, resulting in the release of preformed mediators such as histamine and tryptase, mediators newly synthesed such as PLD_2, LTC_4 and PAF, as well as cytokines and chemokines. G proteins are involved in the activation of mast cells induced by basic compounds and peptides. Mast cells can also be activated *via* the complement activation pathways.

2. Pseudo-allergic reaction caused by direct mast cell activators

Mast cells can be activated *via* several different mechanisms, among which is the classical pathway known as IgE-mediated mast cell activation, which is triggered by the cross-linking of FcεR1 receptors with antigen-specific IgE (*10*). Mast cell activation can also be completed in an IgE-independent manner using commercially available activators, such as opioid drugs, basic secretagogues, and calcium ionophores.

Upon activation, the degranulation reactions of mast cells are induced: (*i*) Performed mediators stored in granules are released, including histamine, tryptase, heparin and serotonin, which are responsible for most of acute effects of mast cells (*11-14*); (*ii*) Lipid-derived mediators are newly synthesized, such as prostaglandin D_2 (PGD_2), leukotriene C_4 (LTC_4) and platelet-activating factor (PAF), which mediate other relatively subacute functions of mast cells (*15-17*); (*iii*) Cytokines and chemokines (*18*) (Figure 1).

2.1. *By opioid drugs*

Opioid drugs have been widely used for the treatment of pain for thousands of years. Since they are such

commonly used drugs, adverse reactions are a concern. For example, morphine, codeine, and meperidine hydrochloride have been reported to induce mild pseudo-allergic reactions *via* the direct activation of mast cells (*19*,*20*). Moreover, some endogenous opioid peptides such as dynorphin, [D-Ala^2-D-Leu^5] enkephalin, β-endorphin, and morphiceptin have also been demonstrated to induce activation of skin mast cells (*21*).

It has been established that pseudo-allergic reactions caused by opioid drugs result from activation of opioid receptors present on mast cells (*21*,*22*). Moreover, opioid receptor activation has been proved to be associated with phospholipase C linked transduction mechanisms (*23*). Furthermore, one of the main mechanisms of mast cell degranulation has been shown to be activation of phospholipase C-linked pathways (*24*). As a result, we can assume that activation of mast cells induced by opioid drugs may be attributed to a phospholipase C-linked mechanism.

2.2. *By basic secretagogues*

Mast cells can be activated directly by a lot of polycationic molecules collectively known as the basic secretagogues, including naturally occurring polyamines such as hymenoptera venoms, various amines such as compound 48/80, and positively charged neuropeptides such as substance P (*25*).

Hymenoptera venoms are complicated mixtures of pharmacologically and biochemically active compounds such as peptides, proteins and biogenic amines, which may induce severe pain, local tissue damage and even death. Mastoparan, obtained from wasp venom, is an amidated tetradecapeptide responsible for the activation of mast cells and the release of histamine (*26*). The regulatory mechanism of mastoparans may be associated with the modulation of proteins including phospholipase A2 and phospholipase C (*27*,*28*). Moreover, some mastoparans are reported to bind G-protein coupled receptors (GPCRs), resulting in activation of mast cells (*29*,*30*). [Lys^{10}, Leu^{13}] mastoparan, another tetradecapeptide from wasp venom toxin, has been found to have the same mast cell activation role as mastoparan, and it is a much better tool for study of the mechanism of mast cell degranulation and intracellular signal transmission (*26*). What is more, it has been discovered recently that two novel mastoparan peptides (Polybia-MP-II and -III) from the venom of the neotropical social wasp *Polybia paulista* can also trigger activation of mast cells (*31*).

Compound 48/80, a condensation product of phenethylamine cross-linked by formaldehyde, is known as one of the most potent secretagogues of mast cells. It can strongly activate cellular exocytosis, causing a rapid release of allergic mediators such as histamine. As a result, it has been widely used to study the mechanism of anaphylaxis (*32*). Activation of mast cells induced by compound 48/80 is reported to be associated with phospholipase D and heterotrimeric GTP-binding proteins (*33*). Besides, compound 48/80 can activate trimeric G proteins, and mainly those of the Gi or Go categories (*34*,*35*).

It is well-known that mast cells and basophils are both significant participants in allergic diseases, but the effect of compound 48/80 on basophils is less certain. Degranulation of basophils has been studied both *in vivo* and *in vitro* after exposure to compound 48/80. Shelley and Juhlin observed degranulation of normal human basophil leucocytes in the presence of the compound (*36*), while Haye *et al*. were unable to confirm that result with basophils from eight patients with non-allergic urticaria (*37*). Marks *et al*. failed to demonstrate such *in vivo* degranulation in cockerels and rabbits, either (*38*).

Substance P (SP), an 11-amino acid peptide member of the tachykinin family, plays a significant role in immunological and inflammatory states, and is a mediator of asthma, tissue injury, arthritis, allergy and autoimmune diseases (*39*). Neuropeptide SP has been shown to trigger activation of mast cells and results in selective secretion of abundant mediators, such as cytokines and chemokines (*40*). The mechanism involved may be that SP can directly activate pertussis toxin (PTX)-sensitive G proteins (such as Gi_2 and Gi_3) in mast cells, mobilizating phospholipase Cb that causes exocytosis, and stimulating phosphatidylinositol 3-kinase that induces synthesis and release of arachidonic acid metabolites (*41*). What's more, it has been established that mast cell activation induced by SP proceeds through the neurokinin-1 receptor (NK1R) of G proteins (*42*), which mediates the main biological effects of SP. SP has also been shown to induce NK-1 receptor-independent activation of mast cells, which is associated with activation of the MrgX2 receptor (*43*), a member of the G protein-coupled receptor (GPCR) family (*44*).

2.3. *By calcium*

Calcium is known as a key second messenger in immunologic responses and degranulation processes of mast cells and basophils (*45*,*46*). The regulation of cytoplasmic calcium levels on mast cell secretory activity requires the introduction of calcium ionophores. For example, calcium ionophore A23187, a mobile-carrier of divalent cations such as Ca^{2+}, Mg^{2+}, and double H^+ (*47*,*48*), can reduce the level of Ca^{2+} stored in mitochondria or increase the inflow from the extracellular medium (*49*,*50*), resulting in the elevation of the cytosolic Ca^{2+}, which can induce mast cell exocytosis and release of histamine. The mechanism involved in the role of calcium ionophore A23187 may be based on the two following aspects:

(*i*) The release of Ca^{2+} from internal stores has been reported to be associated with some second messengers, including phospholipase C, phospholipase D, inositol 1,4,5-triphosphate (IP_3), and diacylglycerol (DG) (*51*). (*ii*) Degranulation dependent on the influx of extracular Ca^{2+} may be related to the members of the SNARE (soluble NSF attachment protein receptor) family, such as SNAP-23 (synaptosome-associated protein of 23 kDa), syntaxin, synaptotagmin, and molecules of the VAMPs (vesicle-associate membrane protein) family which regulate the granuleto-granule or granule-to-plasma membrane fusion process (*52*). In addition to Ca^{2+}, Mg^{2+} and Zn^{2+} are also necessary for the activation of mast cells (*53*).

3. Pseudo-allergic reaction caused by complement activators

More than 30 complex components are included in the complement system of the human body, which play significant roles in defense against infection, distinction between innate and adaptive immunity, and repairing injured tissues (*54,55*). Due to imbalance or deficiency of the complement regulating system, diseases may be caused by complement activation, such as complement activation-related pseudo-allergy (CARPA) (*56*). It is suggested that the complement system can be activated by some drugs and excipients, resulting in production of anaphylatoxins such as C3a, C4a, and C5a (*56*). They can bind to the complement receptors C3aR, C4aR, and C5aR, respectively, on the surface of membranes, and stimulate degranulation of serosa mast cells and peripheral blood basophils (*57*). The complement system is activated by three different pathways: the classical pathway, the mannose-binding lectin pathway and the alternative pathway (Figure 2) (*58*), which are different at the stage of C3 component activation in the most significant moment of system activation (*59*).

Known examples of CARPA are caused by liposomes (*60*), radiocontrast media (RCM) such

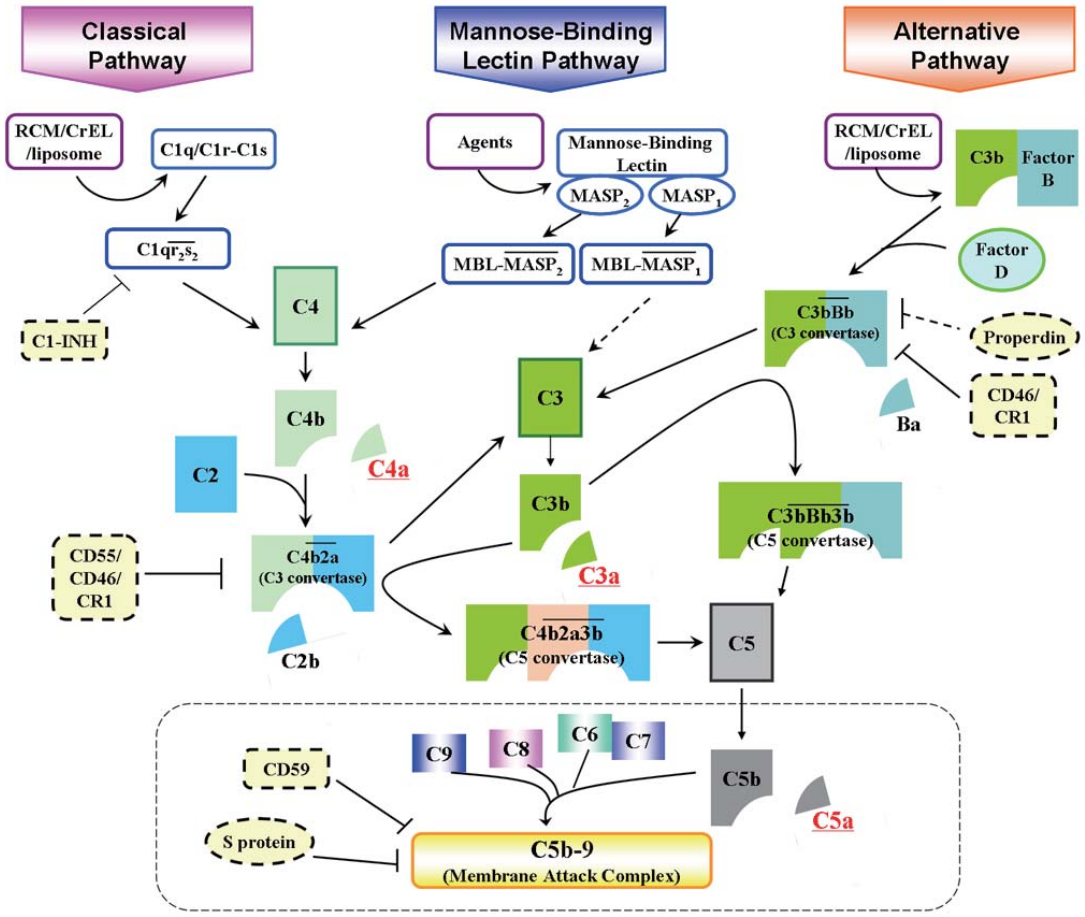

Figure 2. Pathways of complement activation. The complement system can be activated *via* three different pathways: the classical pathway, the mannose-binding lectin pathway and the alternative pathway. All three pathways cleave C3 and form membrane attack complex (MAC) C5b-9 eventually. $C1qr_2s_2$ complex is the promoter of the classical pathway and mannose-binding lectin-$MASP_1$/$MASP_2$ is the promoter of the mannose-binding lectin pathway. Both cleave C4 to C4a and C4b, the latter binding to fragment of C2, forming the C3 convertase of the classical and mannose-binding lectin pathway. Besides, MASP1 could cleave C3 directly. The alternative pathway is started by the forming of C3b-Bb complex (C3 convertase), by which C3 can be hydrolyzed to C3a and C3b, the latter can bind to C3 convertase and C5 convertase is formed. C5 convertase cleaves C5 to C5a and C5b, resulting in the same cause and end effect.

as metrizamide, iohexol, iopamadol, ioversol and ioxaglate (*61,62*), adjuvant amphiphilic emulsifier solvent systems such as Cremophor EL(CrEL) in Taxol (*63*) and so on.

3.1. *By liposomes*

Liposomes are increasingly used for targeted or controlled release of many diagnostic agents and drugs in medicine. To date, marketed liposomal drugs, such as Doxil (Caelyx) (*64*), Abelcet (*65*), AmBisome (*66*), Amphocil (*67*), and DaunoXome (*68*), have been reported to cause CARPA with morbidity rates varying from 3 to 45 percent. Taking Doxil as an example, the reported incidence changes between 0-25%, with the average value of 8% and the median value of 5% (*69*).

It has been shown that different characteristics of liposomes and experimental conditions can result in different pathways or levels of complement activation, leading to the mechanistic study of CARPA caused by liposomes being difficult (*70*). For example, the characteristics of liposomes such as large size, polydispersity, surface charges and high cholesterol (> 45%) content are all shown to promote the incidence of CARPA (*69*). The results published by Chanan-Khan *et al.* have demonstrated that the complement activation caused by some lipsomes is through the mechanism of an increase of Bb, an active fragment of the alternative pathway (*65*). In addition, the activation of complement systems can also be induced in the classical pathway by direct binding of C1q to complement reactive protein-tagged liposomes or the phospholipid bilayer. S protein-bound C terminal complex (SC5b-9), the terminal complement complex, has been shown to be highly sensitive in predicting CARPA in clinical studies. Therefore, the SC5b-9 assay could be a biomarker for clinical diagnosis and laboratory studies (*71*).

3.2. *By RCM*

Radiocontrast media (RCM), which are widely used in diagnostic radiology or radiotherapy, have been reported to cause adverse reactions with an annual incidence rate of about 2.1-12.66% (*72*), and deaths of 1 to 3 per 100,000 administrations (*73*). For example, sodium iothalamate, a kind of RCM, has been found to induce CARPA in dogs as well as other RCMs, such as metrizamide, iothalamate, diatrizoate, acetrizoate, iodipamide, and iopanoate (*74*). What is more, clinical studies showed that 42 patients out of 220 presented pseudo-allergic reactions after RCM injection, with symptoms appearing in 90 sec and disappearing 30 min later (*75*).

Similarly to liposomes, RCM reactions can be influenced by characteristics of the RCM, including osmolarity, charge, iodine number, administration speeds and the recent constitutional features of patients (*76*). Hirshfeld *et al*. compared nonionic, low-osmolality radiocontrast agents with ionic, high-osmolality agents during cardiac catheterization and found the latter ones could induce adverse reactions more easily (*77*). Moreover, it has been shown that adverse reactions induced by ionic contrast materials are in the range of 4% to 12% while those by nonionic contrast materials are 1% to 3% (*62*). Katayama *et al*., in research with over 300,000 contrast administrations, found the prevalence of severe adverse drug reactions was 0.04% for nonionic contrast media and 0.2% for ionic contrast media (*78*).

A report demonstrates that the intravenous infusion of RCM results in the release of vasoactive mediators, such as histamine and serotonin, which may stem from mast cells or basophils. An increase in plasma histamine levels has also been observed after intravenous administration of RCM in dogs (*79*) as well as in humans (*80*). The mechanism involved seems to be mediated by proteins of the alterative pathway, because the synergistic effect would not be shown in serum without the complement components (*81*). To be specific, the mechanism involved in RCM reactions may be associated with production of C3a and C5a, or suppress complement regulatory factors I and H *in vivo* and *in vitro*, leading to activation of the complement system in both the classical and alternative pathways (*61*).

3.3. *By CrEL*

CrEL, a non-ionic detergent, has been widely used as a vehicle for insoluble drugs, including anticancer agents such as paclitaxel (taxol) and immunosuppressants such as cyclosporine (*82*). The drugs mentioned above dissolved in CrEL may cause severe and even life-threatening CARPA, especially taxol (*83*). It has been demonstrated in a clinical study that an equivalent volume mixture of CrEL and taxol has caused a significant increase of the serum levels of SC5b-9 and Bb fragments, end products of complement activation (*63*).

It has been shown that the complement activation induced by CrEL is mainly through the alternative pathway. One possible mechanism is that CrEL could form non-ionic block copolymer surfactants, L101 and L102, both of which can bind to C3 on the surface of cell membranes and result in activation of the complement alternative pathway (*63*). Other studies revealed that microdroplets with varying sizes up to 300 nm could be formed by CrEL interacting with plasma lipoproteins HDL and LDL. These microdroplets can bind to C3bBb, one of C3 convertases, leading to the release of anaphylactoxin C3a or C5a and the occurrence of pseudo-allergic reactions (*84,85*). In addition, Szebeni *et al.* found that taxol could form 8-20 nm spherical structures in aqueous solutions, and

therefore, Taxol or pure CrEL in aqueous solutions might be eliminated *via* 30 kDa cutoff filters and thus activation of the complement system significantly reduced (*84*).

4. Pseudo-allergic reaction caused by nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a series of substances used to treat pain, fever, or inflammation. They inhibit the function of cyclooxygenases (COXs) which are strong mediators in the conversion of arachidonic acid (AA) into thromboxanes and prostaglandins (PGs). This inhibition leads to the metabolism of AA toward the 5-lipoxygenase pathway and results in an increase of cysteinyl leukotrienes release.

There are two subtypes of COXs: COX-1 and COX-2. COX-1 is a constitutive enzyme present in all cells and is significant in mucosa protection and physiological homeostasis (*86,87*). COX-2 is an inducible enzyme and is expressed only in a limited range of cell types after stimulation by inflammatory signals (*88*). NSAIDs vary in their mechanisms by inhibiting different isoforms of COXs. It has been shown that therapeutic effects of NSAIDs are primarily associated with their abilities to inhibit COX-2, while some of their frequent adverse effects are induced by COX-1 inhibition (*89*).

NSAIDs are reported to induce pseudo-allergic reactions, which are commonly described as intolerant in the medical literature (*90*). Pseudo-allergic reactions to NSAIDs account for 21% to 25% of all adverse drug reactions (*91*). Taking aspirin as an example, intolerance reactions are typically developed with the symptoms of rhinorrhea and conjunctival irritation within one hour after aspirin administration with acute asthma attacks (*92*). Szczeklik published results indicating that aspirin intolerance may be related to inhibition of COX-1, resulting in increased production of leukotrienes and decreased synthesis of PGE2, which is responsible for the symptoms of pseudo-allergic reactions observed in patients (*93*). This theory is also supported by multiple observations, including increased expression of the enzyme LTC_4 synthase (LTC4S) and LT receptors, and increased urinary leukotriene E_4 (LTE_4) levels in this patient population (*94-96*).

5. Nonclinical detection methods

Several animal models have been established to detect pseudo-allergic reactions, including pig, dog, and rat models. Szebeni *et al*. has compared the sensitivity of these models in complement-mediated hypersensitivity reactions to liposomes and other lipid-based nanoparticles, and concluded that pig and dog models were more applicable than rat models in predicting pseudo-allergic reactions of particulate "nanodrugs". Moreover, dogs can also be a model used for micellar lipids (such as CrEL), while pigs cannot (*97*). It has also been indicated that pseudo-allergic shock could be induced in porcine models by intravenous injection of calcium ionophore A23187 (*98*). If symptoms of anaphylaxis are observed in animal studies (as shown in Table 1), the following studies should be considered. Various methods should be studied to distinguish pseudo-allergic reactions from true IgE mediated type I allergy. For example, the mast cell line, as an *in vitro* model, is extensively used to detect the release of histamine induced by drugs (*99*). Among which, rat peritoneal mast cells have been the most popular model for many years (*100*). Besides, biochemical markers of pseudo-allergic reactions should be observed in nonclinical toxicology studies, including the detection of serum anaphylactic complement products in animals which show signs of anaphylaxis (*56*). Careful evaluation of the above reactions may supply valuable information on biochemical markers for clinical trials.

6. Conclusions

Pseudo-allergic reactions, which are mediated in an IgE-independent mechanism, have drawn more and more people's attention recently. Three possible mechanisms involved have been introduced, with the important drugs and agents which have been studied, in considerable detail. However, due to little understanding in this area, there is no rapid *in vivo* or *in vitro* diagnosis test in the clinic. The skin test is used for the diagnosis of type I allergy, but not for the pseudo-allergic reactions. In view of the characteristics of pseudo-allergic reactions, the provocation test may be the only way to come to a diagnosis. With the further study of the mechanism of these reactions, effective diagnosis methods in the clinic will be found.

Acknowledgments

The authors acknowledge Zhao-Hua Liu, Hui-Di Qin for the helpful comments on the manuscript. This work was supported by a Grant from the "Eleventh Five-year Plan" of Key Projects in the National Science & Technology Pillar Program (No. 2009ZX09502-001) and National Natural Science Foundation of China (No. 30973934).

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(Received March 08, 2011; Revised August 15, 2011; Accepted August 26, 2011)