

Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms

Bo Zhang Qin Li Chenyang Shi Xinyue Zhang

Department of Pharmacology, Institute of Materia Medica, Zhejiang Academy of Medical Sciences, Hangzhou, PR China

Keywords

Complement · Drugs · Mast cells · Pseudoallergy

Abstract

Adverse drug reactions occur frequently and can trigger pseudoallergy, which has become a serious threat to public health. Pseudoallergy is a typical non-immune anaphylactic reaction characterized by the independence of antigen-specific immune responses. In the clinic, pseudoallergy is often elicited by the first dose of medication, and here lies its unpredictability and occasional lethal outcome. However, the mechanisms of pseudoallergy are not well understood. This review focusses on the causes and mechanisms of pseudoallergy induced by drugs. Two categories of mechanisms will be considered, namely, (1) complement activation-related pseudoallergy and (2) mast cell activation-related pseudoallergy. The factors that induce pseudoallergy include opioid drugs, complement activation-related pseudoallergenic drugs, nonsteroidal anti-inflammatory drugs and traditional Chinese medicine injections.

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Introduction

Hypersensitivity reactions (HSRs) have been categorized into 4 groups [1]. However, the classification of HSRs by Gell and Coombs has limitations in that pseudo-

allergy cannot be fitted into any of the 4 types [1, 2]. Pseudoallergy is characterized by immediate systemic reactions that are similar to anaphylaxis symptoms, but the mechanisms involved are mediated by the release of mediators from basophils and mast cells that is not triggered by Immunoglobulin E (IgE) [3]. The condition is often elicited by the first dose of medication, which induces mast cells and basophils to degranulate. Pseudoallergy does not elicit antigen-specific immune responses but does evoke histamine release, the activation of the complement system, atypical synthesis of eicosanoids, and the inhibition of bradykinin breakdown [4].

Indeed, pseudoallergy and anaphylaxis are clinically indistinguishable [5]. The signs and symptoms of pseudoallergy are practically identical to IgE-mediated symptoms including angioedema, urticaria, bronchospasm and gastrointestinal signs [6, 7], together with skin flushing, headache, edema, hypotension and shock [8]. Pseudoallergy can be attributed to the direct activation of effector cells and the form of anaphylatoxins produced and may be induced by opioid drugs, complement activation-related pseudoallergenic drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) and traditional Chinese medicine injections (TCMIs).

It has been suggested that two-thirds of HSRs may be attributable to pseudoallergy [9]. Due to the lack of systematic studies of the causes and mechanisms involved in pseudoallergy, the diagnosis and treatment of these reactions remain a significant clinical challenge. Therefore,

this review clarifies some of the possible causes and mechanisms involved in drug-induced pseudoallergy to facilitate clear thinking.

Nomenclature

As early as 1937, the term “anaphylactoid reaction” was used to describe a syndrome caused by the injection of egg white. In 1950, Halpern and Briot described this syndrome in great detail. In 1957, Parratt and West [10] suggested that the anaphylactoid reaction was noted mainly in the rat. However, Ehlers et al. [11] identified the roles of non-allergic HSRs in young people with chronic urticaria. In the 1990s, the terms “pseudoallergy” and “non-allergic hypersensitivity” began to be used frequently. Various authors reported the HSRs as pseudoallergen-induced. The prefix “pseudo-” is commonly used to describe the symptoms that mimic another condition. The clinical symptoms of pseudoallergy have been shown to be similar to those of classical anaphylaxis [12]. It is important that medical terminology is widely understood by all specialists and physicians engaged in different fields of medicine and research. In view of inconsistency in the terminology in the published literature, we believe that “pseudoallergy” should be the preferred term for this condition.

Mechanisms of Pseudoallergy

Although the clinical symptoms of pseudoallergy are quite similar to common allergy or type 1 reactions [12], pseudoallergy is quite distinct from IgE-mediated allergy. The reaction arises for the first time without prior sensitization [13] and different drugs can trigger pseudoallergy by different mechanisms, that is, taxol can induce pseudoallergy by activating the complement system [13].

Complement Activation-Related Pseudoallergy

Anaphylatoxins are the causative factors that trigger complement activation-related pseudoallergy (CARPA). Complement-mediated reactions counter the effects of potentially harmful agents in the body (radiocontrast media, liposomes, NSAIDs, TCMI) through the anaphylatoxin/mast cell/circulatory system axis [1, 14]. The centre of CARPA is the complement system, which causes subsequent reactions in the CAPRA cascade. Molecular and cellular activation and interactions comprise this complicated biochemical cascade. In principle, the processes un-

derlying CARPA consist of 3 steps: (1) the complement system is activated; (2) secretory cells and blood cells are stimulated; and (3) effector cells of CARPA respond to mediator challenges [14]. The initial trigger activates the complement system, which induces the release of the primary mediators. Then, the anaphylatoxins bind to secretory cells (mast cells, basophils, macrophages, other phagocytic cells, and leukocytes) leading to the release/production of a multitude of secondary mediators (including histamine, tryptase, platelet-activating factor, thromboxane A₂, leukotrienes (LTs), cytokines, proteases, and prostaglandins) [14, 15]. The complement cascade can be triggered by the classical pathway (CP), lectin pathway (LP) or alternative pathway (AP) [16] in which complement component 3 (C3) plays an important role (Fig. 1). C3, a protein associated with complement cascades, is critical to the complement system [17]. The membrane attack complex is formed by the activity of these 3 pathways.

Classical Pathway

The CP is triggered by interactions between antigen-antibody complexes on the surface of microorganisms [18]. The proteases C1s are part of the C1 complex. C1s can mediate the generation of CP C3 convertase. C1q binds to Immunoglobulin G (IgG) and Immunoglobulin M promoting cascade progression, which causes C1r and C1s activation. C4 is cleaved into C4b by this protease. Following cleavage of C2, C4b2a is generated, which converts C3 into C3b and forms C4bC2aC3b (C5 convertase) [19–21]. The C3 convertase C4b2a is able to cleave C3 and initiate the amplification of downstream effector functions [22, 23].

Lectin Pathway

The LP involves the activity of mannose-binding lectin (MBL) and ficolins acted pattern-recognition molecule that directly recognizes carbohydrate patterns on the surface of pathogenic microorganism. Each pattern-recognition molecule that assembles with MBL-associated serine proteases (MASPs) has a similar structure to C1r or C1s. On this basis, MASP-2 cleaves C4 and C2, which induce generation of the C3 convertase [22].

Alternative Pathway

The AP of the complement system is an innate component of the immune system, playing an important role in the natural defense against infection. AP is different from CP and LP; AP C3 can be directly activated and can

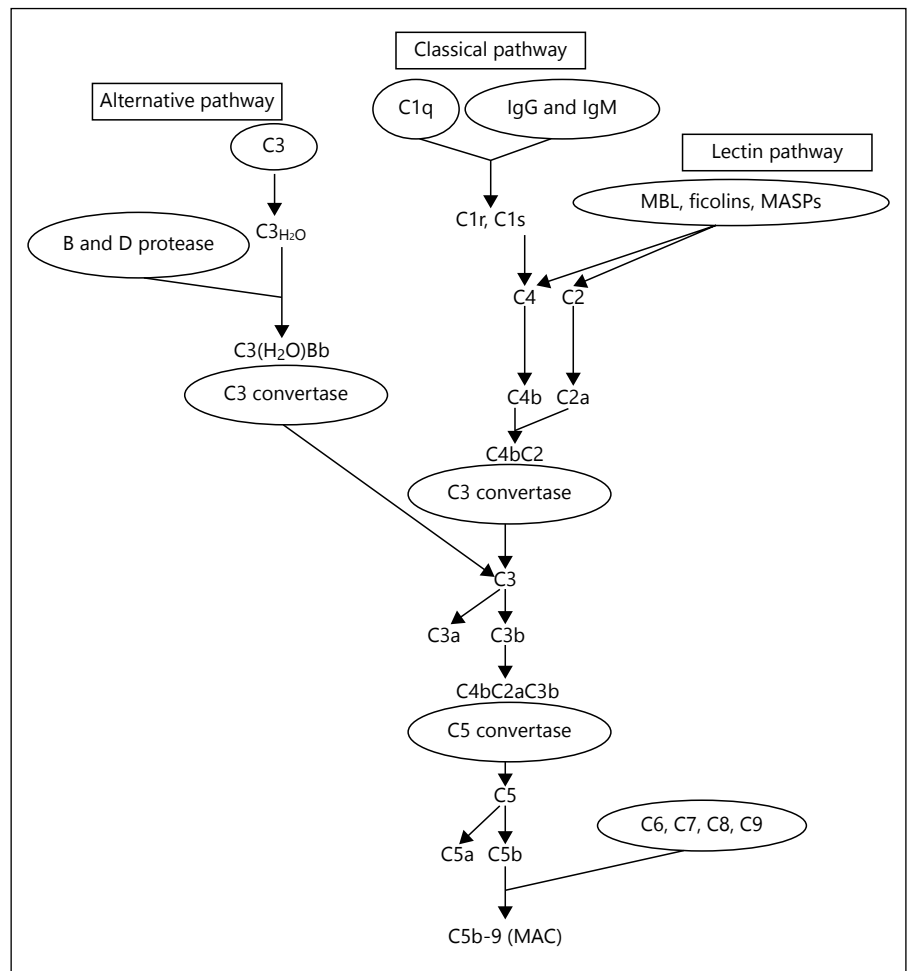


Fig. 1. Classical, lectin and alternative pathways. MBL, mannose-binding lectin; MASPs, MBL-associated serine proteases; MAC, membrane attack complex.

accomplish the chain reaction from C5 to C9. The factor B and D protease can bind the hydrolyzate C3(H₂O), which is a hydrolyzing C3 molecule. This binding generates C3 convertase C3(H₂O)Bb that cleave C3 into C3a and C3b fragments [22, 24]. The C3b induces formation of AP C5 convertase. The convertase cleaves C5 into anaphylatoxin C5a and fragments C5b. Finally, the C5b plays an important role in the cascade (C6, C7, C8, C9) [19, 25].

Mast Cell Activation-Related Pseudoallergy

In multifarious pathological and physiological processes, mast cells that release differential mediators play very important roles. In non-IgE-mediated anaphylactoid reactions, various components (IgG, complement components, neuropeptides, cytokines, chemokines, and other inflammatory products) [26–30] directly stimulate the degranulation of mast cells and the selective release of mediators. Besides these endogenous stimuli, some exogenous molecules, which

cause drug side effects can also directly activate mast cells [31], such as a vitamin K₁ injection or a Qingkailing injection [32, 33]. Different from IgE-mediated allergy, which is mediated by cell-surface receptors, the drugs are able to induce mast cell degranulation and alter enzymatic activity through various pathways [34, 35]. Cysteinyl LTs (cysLTs) and histamine, released by mast cells, mediate bronchoconstriction [36].

Stimulation via Exogenous Molecules

Mast cells can be activated directly by many small molecular weight drugs. The activation is often associated with systemic pseudoallergenic and peptidergic drugs [29, 34]. It has been reported that some exogenous molecules, such as compound 48/80, can stimulate phospholipase D activity. Phospholipase D gives rise to the generation of endogenous phospholipids, which activate the lysophosphatidic acid receptor [32]. This property con-

Table 1. Drugs causing pseudoallergy

Opioid	Liposomal	Micelle-solubilized	NSAID	TCMIs	Other
Morphine	Abelcet	Cyclosporine	Aspirin	Shuanghuanglian injection	Vitamin K ₁ injection
Codeine	Ambisome	Elitec	Dolobid	Potassium dehydroandrogropolide succinate injection	Rocuronium
Meperidine	Amphocyl	Etoposide	Toradol	Shenmai injection	
Hydrocodone	Daunoxome	Fasturec	Lodine	Qingkailing injection	
Hydromorphon	Doxil	Taxol	Voltaren	Xuesaitong injection	
Oxycodone	Caelyx	Taxotere	Motrin	Danshen injection	
Methadone	Myocet	Vumon	Naprosyn	Andrographis injection	
Fentanyl	Visudyne		Ansaid		
Buprenorphine					

tributes to G protein-activation. The activated G proteins can produce exocytosis from mast cells, the synthesis of phosphatidylinositol 3-kinase, and the formation of arachidonate metabolites [31, 37]. The stimulus of phosphatidylinositol 3-kinase activates phospholipase C gamma, which in turn invokes the hydrolysis of phosphatidylinositol 4,5-bisphosphate generating inositol 1,4,5-trisphosphate and diacylglycerol. These mediators induce an increase in the level of intracellular Ca²⁺, which in turn activates protein kinase C [35]. This series of reactions causes mast cell degranulation and the release of inflammatory mediators generated by the PTK-PLA2 pathway [31].

Stimulation via Complement Factors

Complement is activated and anaphylatoxins are formed during pseudoallergy. C3a and C5a can induce respiratory distress, which results from the constriction of smooth muscle in the bronchioles and pulmonary arteries, and aggregation of leukocytes and platelets in the pulmonary blood vessels. C3a and C5a produce their effects by binding to specific C3a receptor (C3aR) and C5a receptor (C5aR), respectively. C3aR and C5aR proteins and mRNA are expressed by bronchial smooth muscle and epithelial cells in both mouse and human lung [38]. Moreover, mast cells express C3aR and C5aR, which are 7 transmembrane domain G protein-coupled receptors [27]. C3a and C5a are mediated via the activation of their respective G protein-coupled receptors in mast cells [27, 39, 40]. It has been reported that C3a activates mast cells either via the activation of mast cell surface G

protein-coupled receptors when the C3a level is low, or via the direct activation of G proteins when the level is high [27, 41]. It has been demonstrated that C3a, which can give rise to extracellular signal regulated kinase and AKT phosphorylation, causes a robust degranulation and activates different signaling pathways to induce chemokine production in human mast cells [42]. The anaphylatoxins C3a and C5a have high activity in stimulating chemotaxis and mobilization of intracellular free Ca²⁺ in mast cells [43]. C5a causes the rapid release of histamine and tryptase from mast cells, which can be activated in vitro by therapeutic and diagnostic agents [44].

Drug-Induced Pseudoallergy

It should be mentioned that some agents (Table 1), such as liposomal drugs [14], vitamin K₁ injection [32] and TCMI, can induce pseudoallergy, though some investigators believe that the reactogenicity of liposomal drugs is overlooked, as they are not standard entries in approved lists of pseudoallergenic drugs [14]. It has been confirmed that the reactions caused by liposomal drugs are not IgE-mediated but rather via CARPA.

Opioid Drugs

Opioid medications are typically used to treat fracture-associated pain but have well-known adverse effects [45]. Nearly all opioids can cause pseudoallergy by a mechanism that directly triggers mast cell degranulation [46,

47]. It has been reported that opioid drugs, such as codeine, meperidine and morphine can induce pseudoallergy [48]. Opioids induce histamine release by directly activating mast cells and cause flushing or pruritus that is nearly always mislabeled as allergy symptoms [49]. It has been found that codeine and morphine are more prone to inducing mast cell degranulation than other opioids [50]. Codeine induces pseudoallergy via a non-immunologic mechanism, which is independent of both IgE and the high-affinity IgE receptor FcεRI [51, 52]. The activation of mast cell degranulation by codeine may, therefore, occur through its actions at the opioid receptor [51]. There are 3 recognized types of opioid receptors, namely, mu (μ), delta (δ), and kappa (κ) [53, 54]. It has been demonstrated that human mast cells express mRNA for δ- and μ-receptors but not for κ-opioid receptors [51]. Human cutaneous mast cells possess opioid receptors, which when stimulated trigger degranulation. These receptors are activated by the μ-receptor agonists – morphine, codeine and meperidine [55]. There are 2 known pathways that stimulate the degranulation of mast cells: direct G protein-activation and activation through opioid receptor stimulation [56]. Activation of these receptors triggers intracellular signaling pathways mediated by G proteins, ion channel modulation and mitogen-activated protein kinase activation [51]. Codeine preferentially activates the μ-receptor, but the synthetic analog of codeine, meperidine, does not activate human mast cell mediator production at the same doses [51]. The morphine-induced wheal-and-flare response is caused by the activation of a naloxone sensitive μ-opioid receptor on mast cells [55]. Opioid drug-induced stimulation of mast cells is associated with phospholipase C activity attributed to opioid receptor activation [48, 57].

Complement Activation-Related Pseudoallergenic Drugs: Liposomal Drugs and Micelle-Solubilized Drugs

CARPA can be a severe syndrome involving several cardio pulmonary symptoms that include pulmonary edema, hypotension, arrhythmia, airway occlusion, respiratory distress, and potential cardiac arrest, which may eventually lead to anaphylactic cardiogenic shock and death in severe cases [16]. Intravenous injection of nanotechnology drugs (liposomal, micellar) may induce CARPA [14]. Liposomal drugs can also activate CARPA. Liposome activation of AP occurs through mechanisms independent of antibodies through direct C3 adsorption and altered conformational changes that resemble C3b, ultimately triggering the production of C3Bb convertase

[58]. The CP activated by liposomes involves 3 mechanisms: (1) antibodies (IgG and Immunoglobulin M) attaches to the phospholipid head-groups and cholesterol attaches to vesicles; (2) direct C1q binds to liposomes with high-density anionic charges derived from phospholipids; and (3) liposomal activation of the CP via C-reactive protein binding occurs, which activates the complement system by acting on the globular head of C1q [58]. Liposome-mediated activation of LP has been rarely reported. MBL binding to phosphatidylinositol-incorporated liposomes presumably induces MASP-2 activation and the triggering of the complement system [58]. The most well-known liposomal drugs are ambisome and doxil, and the micelle-solubilized-drug taxol [14]. Ambisome, a charged non-PEGylated liposome, induces CARPA via AP [16, 59]. Factor H inhibits complement activation induced by the antifungal drugs ambisome and taxol [16]. Doxil, one of the PEG-PL-engineered nanomedicines, triggers the complement activation in human serum through both CP and AP [21]. In addition, PEG may act directly on complement proteins and suppress protein adsorption [21].

Non-steroidal Anti-Inflammatory Drugs

NSAIDs alleviate inflammation (swelling) and pain (analgesia) by inhibiting different isoforms of cyclooxygenases (COXs) and by reducing the synthesis of prostaglandins. COX-1 plays an important role in mucosal protection and physiological homeostasis [48]. It has been shown that the adverse effects of NSAID are induced by COX-1 inhibition [60]. Aspirin and single-dose NSAIDs induce pseudoallergy, but some NSAIDs are well tolerated [3]. Unexpectedly, the use of acetic and propionic derivatives has a relatively high risk for developing anaphylactic reactions [61]. For instance, aspirin inhibits COXs by converting arachidonic acid to various prostanooids, resulting in the synthesis of LTs and a decreased synthesis of prostaglandin E₂ [47, 48]. NSAIDs inhibit the function of COX, which directs the metabolism of arachidonic acid towards the 5-lipoxygenase pathway, resulting in an increase of cysLT synthesis [62]. Two types of LTs are formed by the 5-lipoxygenase-mediated oxidation of arachidonic acid into the unstable intermediate, LTA₄, namely, cysLT and LTB₄. CysLTs are generated in mast cells and basophils when LTA₄ is conjugated to form reduced glutathione by LTC₄ synthase. The cysLT, LTC₄, is extracellularly converted into LTD₄ and then to cysLTs, a stable metabolite, which acts on G protein-coupled LTE₄ receptors to induce bronchoconstriction, vascular leakage and eosinophilia [63, 64].

Traditional Chinese Medicine Injections

Due to high bioavailability, TCMIs are widely used for treatment. However, pseudoallergy is frequently induced by TCMs. Previous studies revealed that TCMIs can directly induce β -hexosaminidase and histamine release through mast cell degranulation [65]. Due to the complexity of the TCMI components, it is important to screen and identify allergenic constituents contained in TCMIs. It has been reported that Tween-80, known as a dispersing agent and solubilizer in TCMI, induces pseudoallergy in zebrafish [66]. Here, the Xuesaitong injection is employed as a typical example of TCMIs. Mediators such as histamine and β -hexosaminidase released from mast cells and RBL-2H3 cells are stimulated by Xuesaitong injection [67]. Xuesaitong-induced pseudoallergy occurs via direct stimulation, the complement and the kallikrein-kinin pathways [68]. In addition, substances that induce an anaphylactoid effect induce histamine, LTB₄, uric acid and other drugs, which have been confirmed to be involved in arginine and proline metabolism [68].

Other Drugs

In addition, it has been shown that vitamin K₁ injections induce pseudoallergy but not anaphylaxis [32]. However, vitamin K₁ itself does not induce pseudoallergy; the trigger may be the solubilizer. Perioperatively administered rocuronium can induce pseudoallergy via the non-IgE mediated Mas-related G protein-coupled receptor member X2, which activates mast cell degranulation [69].

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Conclusions

Pseudoallergy is mediated through IgE-independent mechanisms, which has received much research attention of late. This review has shown that many drugs widely used in the clinic can cause severe, occasionally lethal, pseudoallergy, which still remains an unsolved public health issue. Advances in this field will ensure the safety of new drugs in terms of preventing adverse reactions. Two main mechanisms are summarized in considerable detail, providing guidelines for the ultimate eradication of pseudoallergy. The screening method of components in medications should be further improved. More discussion and research in this field will contribute to the development of effective diagnosis methods in the clinic.

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Disclosure Statement

The authors declare that they have no competing interests.

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