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Submitted on 19 Dec 2017

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Title: The pathophysiology of anaphylaxis

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Declaration of funding sources:

L.L.R. acknowledges support from the European Commission (Marie Skłodowska-Curie Individual Fellowship H2020-MSCA-IF-2014 656086) and the Institut National de la Santé et de la Recherche Médicale (INSERM); S.J.G. acknowledges support from National Institutes of Health grants U19 AI104209, NS 080062, and R01 AR067145 and the Department of Pathology, Stanford University School of Medicine.

Abbreviations used:

ASA: Active systemic anaphylaxis
CysLT: Cysteinyl leukotriene
DT: Diphtheria toxin
DTR: Diphtheria toxin receptor
HDC: Histidine decarboxylase
Ig: Immunoglobulin
LT: Leukotriene
mAb: Monoclonal antibody
MCPT: Mast cell protease
MPO: Myeloperoxidase
OVA: Ovalbumin
PAF: Platelet-activating factor
PAF-AH: Platelet-activating factor acetylhydrolase
PAFR: Platelet-activating factor receptor
PCA: Passive cutaneous anaphylaxis
PGD$_2$: Prostaglandin D$_2$
PSA: Passive systemic anaphylaxis
Abstract
Anaphylaxis is a severe, systemic hypersensitivity reaction that is rapid in onset and characterized by life-threatening airway, breathing, and/or circulatory problems, and that is usually associated with skin and mucosal changes. Because it can be triggered in some people by minute amounts of antigen (e.g. certain foods or single insect stings), anaphylaxis can be considered the most aberrant example of an imbalance between the cost and benefit of an immune response. This review will describe current understanding of the immunopathogenesis and pathophysiology of anaphylaxis, focusing on the roles of IgE and IgG antibodies, immune effector cells, and mediators thought to contribute to examples of the disorder. Evidence from studies of anaphylaxis in humans will be discussed, as well as insights gained from analyses of animal models, including mice genetically deficient in the antibodies, antibody receptors, effector cells, or mediators implicated in anaphylaxis, and mice which have been “humanized” for some of these elements. We also will review possible host factors which may influence the occurrence or severity of anaphylaxis. Finally, we will speculate about anaphylaxis from an evolutionary perspective, and argue that, in the context of severe envenomation by arthropods or reptiles, anaphylaxis may even provide a survival advantage.
Introduction

The recent “International Consensus on (ICON) Anaphylaxis” described anaphylaxis as “a serious, generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal”.\(^1\) This definition is intentionally “generic”, in that it doesn’t mention any of the specific immune elements that might be involved in particular instances of the disorder, as these may vary depending on individual circumstances. In this review, we will describe the key immune elements, such as antibody isotypes, effector cells, and biological mediators, which can contribute to development and pathophysiological manifestations of anaphylaxis. We in particular will note the extent of evidence implicating these immune components in anaphylaxis in humans versus that induced in mouse models of the disorder, focusing especially on forms of anaphylaxis induced by the reactions of allergens with antigen-specific antibodies. We will not extensively review forms of anaphylaxis induced by the antibody-independent activation of effector cells such as mast cells and basophils, topics which have been reviewed elsewhere.\(^2,3\)
Clinical Anaphylaxis

The clinical definition, classification, nomenclature, and treatment of anaphylaxis have been points of controversy, varying among different medical subspecialties and in different countries, and it became clear that an important goal for the field would be to achieve a true international consensus on these important points. Subsequently, multinational, multidisciplinary symposia were convened to agree on the definition of anaphylaxis, the clinical criteria for its diagnosis, and its management. Participants agreed on a description of anaphylaxis as “a serious allergic reaction that is rapid in onset and may cause death”, as well as on three sets of clinical criteria to diagnose anaphylaxis. These criteria were re-affirmed in the recent “International Consensus on (ICON) Anaphylaxis” and are more extensively reviewed elsewhere in this issue (Castells et al.).

A minority of patients exhibit biphasic allergic reactions, in which signs and symptoms of anaphylaxis recur hours after the early phase of the reaction has waned, and in some patients late phase reactions occur without initial hypotension or airway obstruction. In addition to the biphasic reactions observed in some patients with anaphylaxis induced by a variety of causes, patients who have IgE reactive with the oligosaccharide galactose-alpha-1,3-galactose (“alpha-gal”), which is present in mammalian meat and in some therapeutic antibodies, can exhibit anaphylaxis after a delay of several hours during which no signs or symptoms are apparent.

Although there is broad consensus on many aspects of the treatment of anaphylaxis, such recommendations are based largely on observational studies, extrapolation from retrospective case reviews, and a few clinical trials. Injectable epinephrine is universally agreed upon as the first line therapy for anaphylaxis, and may counteract many pathophysiological changes in anaphylaxis by acting through: alpha-1 adrenergic receptors to induce vasoconstriction, which prevents or diminishes tissue/airway edema, hypotension and distributive shock; beta-1 adrenergic receptors to increase heart rate...
and cardiac contractility; and beta-2 adrenergic receptors to dilate airways. In addition, epinephrine’s action on beta-2 adrenergic receptors may potentially block further release of mediators (histamine and eicosanoids) by mast cells and perhaps other effector cells.

Other therapies should be considered second line – and not a substitute for epinephrine. Guidelines generally agree that patients should be placed in a supine position and given crystalloid to maintain perfusion, and oxygen. H1 and H2 antihistamines may be helpful in treating cutaneous and upper respiratory signs and symptoms, and corticosteroids may help to prevent biphasic reactions, but neither prevent nor treat airway obstruction or circulatory collapse and therefore can’t be considered as alternatives to epinephrine.

Development of novel therapies for anaphylaxis is likely to be guided mainly by limited data from humans and by observations made using animal models.

Immunological mechanisms of anaphylaxis

Only limited data on immunological mechanisms of anaphylaxis from human subjects are available due to the life-threatening nature of anaphylaxis and obvious ethical concerns. Human studies of anaphylaxis have included inducing anaphylaxis in volunteers (most often through hymenoptera sting challenge) and collecting samples from patients presenting for emergency management of anaphylaxis. Data obtained in such studies, as well as key findings obtained using mouse models of anaphylaxis, are summarized below, in Figure 1 and in Table 1. The major pathophysiological changes observed during anaphylaxis, and some of the mediators that are thought to contribute to them, are shown in Figure 2.

Effector molecules and receptors

IgE-dependent anaphylaxis
IgE antibodies undeniably can play an important role in conferring immunological specificity to effector cell activation in anaphylaxis and other allergic diseases.\textsuperscript{15-18} IgE is by far the isotype found at the lowest concentrations in the circulation (50-200 ng/ml total circulating IgE in healthy individuals vs. \textasciitilde{}10 mg/ml for IgG),\textsuperscript{15} however, IgE can be found at much higher levels in individuals with allergic diseases.\textsuperscript{16, 19} IgE binds to the high affinity receptor, FceRI, on the surface of blood basophils and tissue resident mast cells,\textsuperscript{20} and (in humans to a greater extent than in mice) other cell types, including neutrophils, eosinophils, monocytes and dendritic cells, and platelets.\textsuperscript{20} Upon exposure to a bi- or multi-valent allergen, crosslinking of FceRI-bound IgE induces activation of mast cells and basophils, and the immediate release of preformed mediators such as histamine and various proteases, as well as \textit{de novo} synthesis of many inflammatory mediators such as certain leukotrienes, prostaglandins, and cytokines.\textsuperscript{16, 20} The importance of that reaction was demonstrated 50 years ago, when different groups realized that purified IgE was capable of transferring skin reactivity from a sensitized human subjects to naive hosts.\textsuperscript{17, 21-23} Similarly, transfer of antigen-specific IgE into naïve mice sensitizes the animals to develop anaphylaxis upon subsequent exposure to that allergen.\textsuperscript{24, 25} Such IgE-mediated anaphylaxis is abrogated in mice lacking the high affinity IgE receptor FceRI\textsuperscript{25}, as well as in mast cell-deficient mice,\textsuperscript{26-28} highlighting the importance of IgE-mediated mast cell activation in such models of anaphylaxis.

Ever since the discovery that IgE can transfer allergen reactivity, the development of antigen-specific IgE antibodies has been regarded as a key risk factor for the development of allergy and/or anaphylaxis upon subsequent antigen exposure. Indeed, quantification of specific IgE levels are used as part of the diagnostic evaluation of those thought to have allergic diseases, and is used to identify potential triggers of anaphylaxis in patients with a
history of anaphylaxis. Several trials have concluded that the use of the anti-IgE therapeutic antibody omalizumab as adjunctive treatment during food or venom immunotherapies can decrease the risks of severe allergic reactions, including anaphylaxis, and in some but not all trials also has been reported to improve the rapidity and efficacy of immunotherapy in achieving desensitization. In addition, limited clinical data also suggest that omalizumab may prevent spontaneous episodes of anaphylaxis in patients with systemic mastocytosis, a disease characterized by marked increases in mast cell numbers and activity (also see the review by Akin et al. in this issue of JACI).

Clearly, however, IgE levels alone do not explain an individual’s susceptibility to anaphylaxis. Some patients can experience near fatal anaphylaxis despite having low or undetectable levels of circulating allergen-specific IgE. Conversely, allergen-specific IgE can be detected in the plasma of many subjects who do not develop clinical symptoms when exposed to that allergen. This is particularly true for hymenoptera venom, where the vast majority (~80%) of people with IgE antibodies specific for hymenoptera venoms have no history of systemic reactions to such venoms. Therefore, the presence of antigen-specific IgE antibodies, taken in isolation, does not indicate that the person necessarily will exhibit any, let alone severe, clinical reactivity to the recognized antigens.

**IgE-independent anaphylaxis**

The fact that some patients experience anaphylaxis despite having undetectable levels of circulating allergen-specific IgE suggests the existence of IgE-independent pathways of anaphylaxis. However, it should be noted that a lack of detection of free IgE does not mean that such patients don’t have enough FceRI-bound IgE to experience IgE-mediated anaphylaxis. More definitive evidence for IgE-independent anaphylaxis has been obtained using mouse models (Table 1).
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Role of IgG and FeγRs

Besides IgE, we now know that mouse IgG also can induce passive systemic anaphylaxis (PSA) reactions, with physiological manifestations similar to those seen in IgE-dependent PSA (mainly hypothermia, vasodilatation and cardiopulmonary changes).\(^{50-60}\) Whether IgG antibodies also mediate anaphylaxis in humans still remains to be proven, and is the topic of a recent review.\(^2\) As demonstrated in mice, IgG-mediated anaphylaxis typically requires a much larger dose of antigen than does IgE-mediated anaphylaxis,\(^61\) and systemic anaphylaxis also requires systemic absorption of ingested antigen.\(^62\) Such conditions could be encountered in the case of anaphylaxis occurring in response to infusion of large quantities of a drug or a therapeutic monoclonal antibody (mAb)\(^2\) (Table 1).

Role of complement

Activation of the complement cascade occurs in response to many stimuli, and leads to generation of small polypeptides: C3a, C4a and C5a, also named anaphylatoxins, which are potent inflammatory mediators.\(^63\) Multiple lines of evidence suggest that anaphylatoxins might be involved in anaphylaxis. Depletion of complement levels and production of C3a and C5a is observed in human anaphylaxis.\(^64, 65\) Anaphylatoxins can activate various myeloid cells, including mast cells and basophils.\(^63\) Injection of low doses of C3a, C4a or C5a into the skin of healthy volunteers induces immediate wheal and flare reactions.\(^66-69\) In addition, one study showed that blood levels of C3a, C4a and C5a correlated with the severity of anaphylaxis in humans.\(^65\) Several transgenic mouse models have been used to study the importance of the complement pathway in anaphylaxis. Data obtained using these transgenic models are reviewed in Table 1, and suggest that, in mice, the effect of complement
components on anaphylaxis may be in most cases largely redundant with that of other mediators and may depend on the specific model used.

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**Potential effector cells of anaphylaxis**

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**Mast cells**

Mast cells are viewed as key players in IgE-dependent allergies and anaphylaxis.\(^1\)\(^6\), \(^7\)\(^0\) Mast cells ordinarily express large numbers of the high affinity IgE receptor, FceRI. During IgE-dependent immune responses, the antigen-dependent cross-linking of antigen-specific IgE bound to FceRI induces the aggregation of FceRI, promoting the activation of downstream signaling events that lead to the secretion of several biologically active products thought to be implicated in allergic reactions, such as histamine and various cysteinyl leukotrienes (Cys-LTs).\(^1\)\(^6\), \(^7\)\(^1\)-\(^7\)\(^3\) The molecular mechanisms of such IgE-dependent stimulation of mast cells have been extensively reviewed.\(^1\)\(^6\), \(^7\)\(^1\)-\(^7\)\(^3\)\(^5\) There is compelling evidence of activation of mast cells during acute anaphylaxis. Although histamine detection can be used to diagnose anaphylaxis (see **Histamine**, below), detection of histamine in clinical blood specimens is difficult due to its extremely short half-life, and histamine isn’t a mast cell-specific product, since it can also be released by other cells, including basophils\(^7\)\(^6\) and neutrophils.\(^7\)\(^7\), \(^7\)\(^8\) Tryptase is much more stable than histamine, and is considered to be a largely mast cell-derived product.\(^7\)\(^9\) Mature \(\beta\)-tryptase is stored in mast cell granules and released upon activation, such as in anaphylaxis, whereas \(\alpha\)- and \(\beta\)-protryptases are secreted constitutively by mast cells and therefore increased blood levels may indicate increased mast cell burden rather than anaphylaxis.\(^7\)\(^9\) Elevated levels of tryptase have been detected during acute anaphylaxis in humans.\(^6\)\(^5\), \(^7\)\(^9\)-\(^8\)\(^2\) However, the roles of tryptase or other mast cell-derived
proteases in anaphylaxis remain unknown. Moreover, in some patients with anaphylaxis, such as children with food allergen-induced anaphylaxis, elevated blood levels of tryptase have not been detected. Additional evidence for a role of mast cells in anaphylaxis comes from the observation that patients suffering from mastocytosis, a disease characterized by the presence of high numbers of mast cells in various organs, have a high occurrence of anaphylaxis. In children with mastocytosis, increased serum tryptase levels, used as an indicator of mast cell burden, is a risk factor for anaphylaxis and for the severity of anaphylaxis episodes. Studies using various strains of mast cell-deficient mice also confirmed the key role of mast cells in IgE-mediated anaphylaxis. Several reports now demonstrate that mast cell-deficient mice also have reduced peanut-induced anaphylaxis in active systemic anaphylaxis (ASA) models. However, the role of mast cells in ASA models using other antigens/allergens is more controversial (summarized in Table 1). Therefore, it is likely that mast cells play either dominant or largely redundant roles in anaphylaxis, and that the mast cells’ role can be enhanced - or masked - depending on the exact model, adjuvant and allergen used.

**Basophils**

Human basophils also express high levels of the high affinity IgE receptor FcεRI, and express the activating IgG receptor FcγRIIA and the inhibitory IgG receptor FcγRIIB. Several lines of evidence suggest that basophils participate in anaphylaxis. For example, IgE-dependent activation of human basophils is associated with elevations in the levels of certain basophil cell surface markers, such as CD203c or CD63, and this forms the basis of “basophil activation tests” which can be used to diagnose or confirm allergen sensitization, and to monitor the effects of efforts to treat these conditions with immunotherapy. However, it is difficult to ascertain how important a contribution basophils make to the
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pathology of anaphylaxis in humans, given the concomitant mast cell activation that occurs in this setting. Even in mice, the role of basophils in anaphylaxis is unsettled (Table 1).

Monocytes/macrophages

Monocytes and macrophages express high levels of activating FcγRs, and can also respond to anaphylatoxins. Studies in mice have shown that depletion of monocytes/macrophages using clodronate liposomes can reduce anaphylaxis in both IgG-mediated passive models and active models (Table 1). These data suggest that monocytes/macrophages might play an important role in anaphylaxis. However, to the best of our knowledge, the extent to which monocytes/macrophages can contribute to anaphylaxis in humans has not yet been determined.

Neutrophils

The potential functions of neutrophils in anaphylaxis have been recently reviewed in detail. Human and mouse neutrophils express several activating FcγRs, can produce histamine, and can release platelet-activating factor (PAF; please see below for details on the role of PAF in anaphylaxis) in response to stimulation with immune complexes in vitro.

Moreover, human neutrophils reportedly can express FcεRI, particularly in some patients with asthma. The major enzyme stored in neutrophils is myeloperoxidase (MPO). A recent report shows that circulating MPO levels are increased in patients with anaphylaxis as compared to healthy donors. Consistent with this, elevated MPO activity can also be detected as soon as two minutes after antigen challenge in an active mouse model of anaphylaxis. However, it should be noted that these results do not provide definitive proof of neutrophil activation in anaphylaxis, since MPO could also be potentially released by other...
cell populations, including macrophages. Reduced expression of the activating IgG receptors FcγRIII and FcγRIV on mouse neutrophils occurs after IgG-mediated PSA, which suggest more definitely that neutrophils could be directly activated by IgG immune complexes during anaphylaxis. Antibody-mediated neutrophil depletion can reduce anaphylaxis in IgG-mediated PSA and mast cell-independent ASA models. However, neutrophil-depleting antibodies had no effect in a mast cell-dependent ASA model induced without artificial adjuvants. This suggests that neutrophils may be particularly prominent in ASA models induced with adjuvants and that such models may not require any non-redundant contributions of mast cells (Table 1).

Platelets

Anaphylaxis in humans is associated with platelet activation, presumably in response to PAF and/or other mechanisms, and activated platelets can release mediators, such as platelet factor 4 (PF4) and serotonin, which might contribute to the pathophysiology of anaphylaxis. Moreover, human (but not mouse) platelets can express FcεRI, FcεRII and FcγRIIA, and platelets can be activated ex vivo following incubation with serum from allergic patients and subsequent exposure to the relevant allergen. Two recent reports have shown that, during basophil activation tests performed in blood specimens ex vivo, basophils (a potential source of PAF) can form associations with platelets, identifying this interaction as one which should be investigated further in the context of anaphylaxis.

Potential mediators of anaphylaxis

Histamine
Histamine has long been considered to be an important mediator of anaphylaxis. Woodrow and colleagues showed that aerosol administration of histamine induces bronchoconstriction in healthy volunteers, although the effect of histamine was much less potent than that of leukotrienes (see Leukotrienes, below). Intravenous administration of histamine in volunteers can reproduce many of the signs and symptoms of anaphylaxis, including cutaneous flushing, headache, airway obstruction and transient hemodynamic changes, mainly represented by systemic hypotension, tachycardia, and increased left ventricular performance. There are four known histamine receptors, named H1-4.

Studies using receptor antagonists suggest that some of the systemic effects of histamine, including airway obstruction and tachycardia, are mainly mediated through H1R, while some others, including cutaneous flushing and headaches, seem to be mediated through both H1 and H2 receptors. H1 antihistamines are commonly used as adjunctive treatment for acute anaphylaxis and anaphylactoid reactions. The contribution of histamine to anaphylaxis has also been confirmed using mouse models (summarized in Table 1). Mast cells and basophils likely represent the main sources of histamine in anaphylaxis. In agreement with that, histamine release is abrogated in mast cell-deficient mice in a model of IgE-mediated PSA, and increases in plasma histamine levels are also abrogated, in two models of ASA, in mice deficient for both mast cells and basophils.

Platelet-Activating Factor (PAF)

PAF is a potent phospholipid-derived mediator implicated in platelet aggregation and thought to play important roles in a variety of immune and inflammatory responses. The biology of PAF and its potential role in anaphylaxis have been recently reviewed in detail. PAF can be released by a variety of human cells, including purified lung mast cells and blood basophils after ex vivo stimulation with anti-IgE antibodies, and by purified neutrophils.
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after incubation in vitro with heat-aggregated human IgG. Many of the cell populations which produce PAF can also respond to PAF, including platelets, mast cells, neutrophils and macrophages (reviewed in ). Injection of PAF in the skin of healthy volunteers induces wheal and flare reactions. Since these reactions could be blocked by H1-antihistamines, it was first proposed that PAF induced wheals via secondary histamine release by dermal mast cells. However, unlike human lung mast cells and peripheral blood-derived mast cells, skin mast cells do not degranulate in response to PAF stimulation ex vivo. In addition, Krause and collaborators showed that intradermal injection of PAF, unlike that of histamine and codeine, did not cause a statistically significant rise in dermal histamine levels in healthy volunteers. A limited number of reports have assessed concentrations of PAF or PAF-acetylhidrolase (PAF-AH) - an enzyme responsible for the rapid degradation of PAF - after anaphylaxis in humans. In these reports, circulating PAF levels were increased and circulating PAF-AH activity was inversely correlated with the severity of anaphylaxis.

The contribution of PAF to anaphylaxis has been studied in more detail using pharmacologic and genetic approaches in mouse models (reviewed in Table 1). In most models, combined inhibition of histamine and PAF almost entirely blocked anaphylaxis, suggesting additive or synergistic effects of histamine and PAF. The main cellular source of PAF in these reports likely depends on the exact anaphylaxis model used. Using an adjuvant-free active anaphylaxis model, we recently reported that the PAFR antagonist CV-6209 can reduce anaphylaxis in wild-type mice, but has no effect on the residual anaphylaxis observed in monocyte/macrophage-depleted mice, suggesting that monocytes/macrophages represent the major source of PAF in this model.

Cysteinyi leukotrienes (CysLTs)
A third class of potential mediators of anaphylaxis was originally termed ‘slow-reacting substance of anaphylaxis’ (SRS-A), and consists of three bioactive cysteinyl leukotrienes (CysLTs): leukotriene B4 (LTB4), LTC4 and LTD4 (reviewed in\textsuperscript{129}). CysLTs are synthesized from arachidonic acid by a variety of cells, including mast cells, basophils and macrophages.\textsuperscript{130} CysLTs and their metabolites can be measured by mass spectrometry, and several reports show that levels of some of these products, namely LTE4, 2,3-dinor-9α,11β-PGF\textsubscript{2}, and 9α,11β-PGF\textsubscript{2}, are increased during the onset of anaphylaxis.\textsuperscript{131-133} While these reports indicate that CysLTs and their metabolites might be good biomarkers of anaphylaxis, they do not prove that these compounds make an important contribution to the clinical manifestations of anaphylaxis. However, multiple observations suggest that CysLTs can promote acute allergic reactions. When injected intradermally in healthy volunteers, each of the three CysLTs elicited a wheal and flare reaction.\textsuperscript{134} In addition, aerosol administration of LTC4 and LTD4 in healthy subjects induced bronchoconstriction with 1,000-fold more potency than histamine\textsuperscript{114,115,129} (Table 1).

More definitive evidence for a role of CysLTs in anaphylaxis comes from studies in mice. Mice deficient for LTC\textsubscript{4}S (a protein responsible for biosynthesis of LTC\textsubscript{4}) or for the Cys-LT receptor CysLT\textsubscript{1}R have markedly reduced IgE-mediated passive cutaneous anaphylaxis (PCA).\textsuperscript{135,136}

Other potential mediators

Anaphylaxis induces changes in levels of many other mediators which could potentially contribute (positively or negatively) to the clinical signs and symptoms (Table 1). This includes tryptase,\textsuperscript{64,80,137-139} prostaglandins\textsuperscript{132,137} and cytokines/chemokines.\textsuperscript{65,138} Depletion of the bradykinin precursor, high molecular weight kininogen, has been observed in anaphylaxis, likely through activation of the plasma contact system and kallakrein.\textsuperscript{64,140,141}
Anaphylaxis patients may also experience depletion of clotting factors, including Factors V and VIII, and in extreme cases develop diffuse intravascular coagulation. While most patients promptly treated for anaphylaxis recover without obvious sequelae, some develop recurrent signs and symptoms which require continued treatment with epinephrine and for which corticosteroids are administered. Such sequelae are thought to reflect the “late” consequences of some of the mediators released by effectors of anaphylaxis, such as cysteinyl leukotrienes, cytokines and chemokines, or by structural cells activated in this setting. Finally, mast cells can release adenosine upon IgE-dependent activation, and adenosine can have complex effects, mediated via various adenosine receptors with distinct functions, which have the potential to influence the pathophysiology of anaphylaxis. However, more work is needed to define the importance of most of these mediators in anaphylaxis, particularly in humans.

Insights from humanized models of anaphylaxis

Several ‘humanized’ mouse models of anaphylaxis have been developed to investigate the functions of human antibodies, Fc receptors and effector cells in anaphylaxis. Transgenic mice expressing human FcεRI instead of the mouse protein (hFcεRI-Tg mice) were generated, and the expression profile of the hFcεRI transgene is very similar to that found in humans. hFcεRI-Tg mice can develop systemic anaphylaxis in response to intravenous sensitization with mouse or human IgE (mouse IgE can bind to human FcεRI, while human IgE can’t bind to the mouse receptor) followed by systemic antigen challenge, cutaneous anaphylaxis when they are sensitized intra-dermally with serum from peanut-allergic patients and then intravenously challenged with peanut extract. hFcγRI-Tg and hFcγRIIA-Tg mice have also been generated, and the expression of hFcγRI or hFcγRIIA in such transgenic mice
recapitulates that found in humans.\textsuperscript{150,151} Each of these transgenic models can develop IgG-mediated anaphylaxis though a mechanism involving monocytes/macrophages and neutrophils.\textsuperscript{122,152} More recently, Gillis and collaborators developed a novel mouse strain in which the human low-affinity IgG receptor locus, comprising both activating (hFcγRIIA, hFcγRIIIA, and hFcγRIIIB) and inhibitory (hFcγRIIB) hFcγR genes, has been \textit{knocked-in} into the equivalent mouse locus.\textsuperscript{153} These \textit{knock-in} mice are susceptible to PSA induced by injection of heat-aggregated human intravenous immunoglobulin (IVIg). The contribution of hFcγRIIA to anaphylaxis is predominant in these mice, as revealed in experiments using an anti-FcγRIIA blocking antibody.\textsuperscript{153} Antibody-mediated depletion of neutrophils, and to a lesser extent basophils, also ameliorated signs of anaphylaxis. Finally, such anaphylaxis also could be partially inhibited using either a PAF receptor antagonist or a histamine receptor 1 antagonist.\textsuperscript{153}

Recently, three groups independently attempted to generate ‘humanized’ models of anaphylaxis using different strains of highly immunodeficient NOD-scid gamma (NSG) mice engrafted with human stem cells.\textsuperscript{154-156} Bryce and colleagues used NSG mice expressing human SCF, IL3 and GM-CSF transgenes (NSG-SGM3 mice), and engrafted them with human thymus, liver, and hematopoietic stem cells. Such engraftment resulted in the development of large numbers of ‘human’ mast cells in NSG-SGM3 mice in the peritoneal cavity and peripheral tissues.\textsuperscript{156} The authors could induce both PCA and PSA reactions upon sensitization with a chimeric IgE containing the human constant region, and challenge with the relevant antigen.\textsuperscript{156} Burton and colleagues used NSG mice carrying a human SCF transgene and engrafted with human hematopoietic stem cells.\textsuperscript{154} The authors demonstrated that such engrafted mice also develop large numbers of ‘human’ mast cells, produce human IgE (hIgE) in response to gavage with peanut extract, and develop anaphylaxis upon subsequent oral challenge with peanut.\textsuperscript{154} Importantly, anaphylaxis in this model could be
blocked in mice treated with the anti-hIgE antibody omalizumab (which does not recognize mouse IgE).\textsuperscript{154} Pagovich et al. also developed a ‘humanized’ model of peanut anaphylaxis in NSG mice engrafted with blood mononuclear cells from patients with peanut allergy with a clinical history of anaphylaxis.\textsuperscript{155} These mice produced human IgE and IgG antibodies in response to intraperitoneal sensitizations with peanut, and developed anaphylaxis upon subsequent oral challenges with peanut.\textsuperscript{155} Again, anaphylaxis was reduced in mice treated with omalizumab, as well as in mice which had received an adeno-associated virus (AAV) coding for omalizumab.\textsuperscript{155}

Altogether, results from such humanized models of anaphylaxis suggest that both hIgE and hIgG have the potential to induce anaphylaxis through their respective Fc receptors, and also suggest that peanut anaphylaxis is highly dependent on IgE.

Genetic diversity/host factors influencing anaphylaxis

Genetic modifiers may influence mast cell activation and the development of anaphylaxis, as demonstrated in differences observed between the 129/Sv and C57BL/6 strains of mice.\textsuperscript{157} 129/Sv mice demonstrated higher levels of plasma histamine than did C57BL/6 mice following anaphylaxis induced by anti-IgE. Although higher numbers of mast cells and serum IgE levels in the 129/Sv mice could potentially explain these differences, the authors also demonstrated that bone marrow-derived cultured mast cells from 129/Sv mice degranulated more robustly than those from C57BL/6 while synthesizing similar quantities of cytokines.\textsuperscript{157} However, the specific genetic modifiers responsible for these observed differences between the two strains of mice remain unknown.

Ethnic differences in rates of food allergy and anaphylaxis suggest that genetic modifiers also may exist in human populations.\textsuperscript{158, 159} Reasons for these ethnic disparities remain unclear, but may reflect true genetic differences, environmental factors, including
socioeconomic status, or a combination of factors. Nevertheless, a handful of genetic polymorphisms have been described that may influence development of anaphylaxis. Genetic polymorphisms in IL-4Rα, IL-10, and IL-13 have been linked to the development of anaphylaxis to drugs and latex\textsuperscript{160-162} but theoretically may influence allergen sensitization more than (or in addition to) effector mechanisms during anaphylaxis.

Polymorphisms affecting metabolism of mediators of anaphylaxis also may influence anaphylaxis severity. As mentioned above, PAF-AH activity levels inversely correlated with severity of anaphylaxis.\textsuperscript{65, 82, 128} A loss of function mutation in PAF-AH, V279F has been linked with asthma, but not yet with anaphylaxis.\textsuperscript{163} Individuals with variants in angiotensinogen, i.e. the MM genotype associated with decreased levels of angiotensinogen, were reported to have increased rates of hymenoptera venom allergy and more severe reactions during venom immunotherapy.\textsuperscript{164} Similarly, amongst patients with tree nut and peanut allergies, lower serum ACE levels were associated with more severe pharyngeal edema, presumably through decreased bradykinin metabolism.\textsuperscript{165}

A few mutations have been described that may influence development and severity of anaphylaxis. An activating mutation in c-KIT, D816V, promotes mast cell proliferation in clonal mast cell disorders including mastocytosis\textsuperscript{166, 167} (also see Akins et al\textsuperscript{36} in this issue of JACI). D816V mutations are also found in some patients with recurrent anaphylaxis who do not have increased mast cell numbers on pathology and therefore do not meet criteria for mastocytosis;\textsuperscript{168} while this suggests that that their mast cells are hyperresponsive, this has not yet been substantiated. In autosomal dominant hyper-IgE syndrome caused by loss-of-function mutations in STAT3, patients have increased levels of total and allergen specific IgEs, but clinically lower rates of anaphylaxis.\textsuperscript{169} This clinical observation may be explained, at least in part, by decreased mast cell degranulation\textsuperscript{169} and/or by inhibition of enhanced
vascular permeability through increased resilience of adherens junctions in patients and cells with STAT3 loss of function mutations.\textsuperscript{170}

The role of sex hormones in anaphylaxis is unclear. Anaphylaxis occurs more commonly in women than men.\textsuperscript{171, 172} Moreover, in a model of PSA, female mice exhibited a greater drop in body temperature than did male mice, and this sex difference could be abrogated by ovariectomy or administration of estrogen antagonist to female mice.\textsuperscript{173}

However, analysis of patients in an anaphylaxis registry revealed an increased severity of anaphylaxis in male versus female patients of 13-56 years of age, but no sex differences in anaphylaxis severity for prepubescent individuals or those older than 56 years old.\textsuperscript{174}

Recovery from anaphylaxis

Many of those who have experienced anaphylaxis and were not treated have survived the episode, particularly those with less severe presentations. What is the basis of such recovery? Variations in metabolism of mediators, including PAF and bradykinin, may influence manifestations of anaphylaxis\textsuperscript{65, 82, 128, 165} and theoretically the ability to recover from these manifestations. In animal models of anaphylaxis and in humans undergoing insect sting challenge, levels of substances with endogenous vasopressor activity, including epinephrine, norepinephrine and angiotensin II, are increased within minutes following development of anaphylaxis,\textsuperscript{175, 176} likely to compensate for the vasodilation and fluid extravasation occurring during anaphylaxis. Observations that beta-adrenergic blockade can exacerbate systemic anaphylaxis in mouse and rat models\textsuperscript{177, 178} and in people with severe anaphylaxis due to multiple causes,\textsuperscript{179-182} particularly when combined with angiotensin converting enzyme (ACE) inhibitors,\textsuperscript{183} support a role for endogenous vasopressors in limiting the severity of pathophysiological changes in anaphylaxis. Mast cell degranulation releases chymase, which can convert angiotensin I to angiotensin II,\textsuperscript{184} and may thereby directly contribute to increased
angiotensin II levels observed following anaphylaxis. In a recent paper, Nakamura and colleagues showed that mice in which mast cells cannot produce prostaglandin D$_2$ (PGD$_2$) have enhanced manifestations of IgE-mediated anaphylaxis. Therefore, it appears that mast cells also can secrete anti-anaphylactic mediators which might help to limit anaphylactic responses.\(^{185}\) Finally, it is possible that genetically-determined or other differences in mast cell activation or mediator release profiles also might contribute to differences in the manifestations of, or recovery from, anaphylaxis.

**Can anaphylaxis be beneficial?**

Using mouse models, we recently reported that the development of a type 2 immune response to honeybee venom (BV) could increase the survival of mice challenged with whole BV\(^{186}\). Also, others have shown in mice that a type 2 immune response to BV phospholipase A$_2$ (bvPLA$_2$, which is considered to be the major BV allergen in humans) could diminish the drop in body temperature induced by challenge with a “near-lethal” dose of bvPLA$_2$.\(^{187}\) Importantly, these effects were dependent on IgE,\(^{186}\) and on the high affinity IgE receptor, FceRI.\(^{186,187}\) In a follow-up study, we also provided evidence that IgE, FceRI and mast cells can enhance the survival of mice injected with Russell's viper venom.\(^{188}\) One of the mechanisms by which innate activation of mouse mast cells can enhance the survival of naïve mice upon their first exposure to various arthropod or reptile venoms is the proteolytic reduction of the toxicity of venom components by mast cell-derived carboxypeptidase 3A or mouse mast cell protease 4 (chymase).\(^{189}\) Given that snake (or arthropod) envenomation in the field can result in systemic distribution of the venom, one could argue that systemic IgE-dependent mast cell activation in this setting could both produce the clinical picture of anaphylaxis and also result in the systemic release of mediators (i.e. mast cell proteases) that can degrade toxic components of the venom. In such settings,
anaphylaxis could be beneficial, if it prevents death by envenomation -- and the unfortunate individual also survives the anaphylaxis. Although we don’t know whether human IgE also can enhance resistance to venoms (and we imagine that we would have some trouble enlisting volunteers for such a study), it is tempting to speculate that anaphylaxis induced by small amounts of venom (e.g. a single or wasp bee sting) represents only the most extreme and maladaptive end of a spectrum of acquired IgE-mediated immune responses to venom that includes, at the other end of the spectrum, appropriately regulated immune responses that can enhance resistance to such venoms.

Concluding remarks

Anaphylaxis represents one of the most urgent of medical emergencies, where rapid diagnosis and prompt and appropriate treatment can mean the difference between life and death. While there has been steady progress in our understanding of the antibodies, effector cells and mediators that can contribute to the development and manifestations of anaphylaxis, especially in the context of mouse models of the disorder, the basic clinical management of anaphylaxis has changed little in decades (see Castells et al. in this issue of JACI) and Table 2. In a report published in 2005, Sampson et al. identified as major research needs both the development of “universally accepted diagnostic criteria” and the importance of identifying “reliable laboratory biomarkers to confirm the clinical impression”. As noted in our Introduction, the first need largely has been addressed by international, interdisciplinary efforts to forge consensus. But the second need remains essentially unfulfilled. It is our hope that further progress in understanding the immunopathogenesis and pathophysiology of anaphylaxis in all of its various forms will help to guide efforts to devise more effective strategies for preventing this disorder and also to provide more effective options for rapidly diagnosing and effectively treating anaphylaxis when it occurs.
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Figure legends

Figure 1. Multiple potential pathways in antibody-mediated anaphylaxis. A. Antigen-specific IgE antibodies and FcεRI-bearing effector cells (e.g. mast cells, basophils) play a dominant role in anaphylaxis induced (sometimes by very small amounts of antigen) when concentrations of IgG antibodies are low. B. Mouse models of anaphylaxis suggest that IgG antibodies and FcγR-bearing effector cells (e.g. basophils, macrophages, neutrophils, as well as mast cells) can be important effectors of anaphylaxis induced by large amounts of antigen in the presence of high concentrations of IgG antibodies. Some examples of anaphylaxis likely involve both pathways (A and B). Note that co-engagement of ITAM-containing activating FcγRs or FcεRI with the ITIM-bearing FcγRIIB (on mast cells [in mice, but perhaps not in humans] or basophils [in humans and mice]) can act to diminish effector cell activation. In red: Strong evidence for the importance of these mediators in human anaphylaxis induced by antigen; in blue: These elements can participate in models of anaphylaxis in mice but their importance in human anaphylaxis is not yet clear; in grey: Elements with the potential to influence anaphylaxis, but their importance in human or mouse anaphylaxis not yet clear (e.g., human mast cells are thought to make little or no serotonin).

Figure 2. Pathophysiological changes in anaphylaxis and mediators that have been implicated in these processes. Note: As mentioned in the text, first line treatment of anaphylaxis consists of the rapid administration of epinephrine (see Castells et al.⁶). Although there is evidence that the mediators shown in the figure, particularly histamine and cysteinyl leukotrienes, contribute to some of the various signs and symptoms of anaphylaxis, and anti-histamines are routinely administered to patients with anaphylaxis, pharmacological targeting
of such mediators represents second line treatment and should not be considered as an alternative to epinephrine. In red: Strong evidence for the importance of that mediator, in humans, in the development of some of the signs and symptoms listed in the adjacent box; in blue: these elements can be important in mouse models of anaphylaxis but their importance in human anaphylaxis is not yet clear (studies in human subjects suggest that cysteinyl leukotrienes may contribute importantly to the bronchoconstriction and enhanced vascular permeability associated with anaphylaxis [see text]); in grey: elements with the potential to influence anaphylaxis, but their importance in human or mouse anaphylaxis not yet clear. Note that some mediators (underlined) are likely to contribute to the development of late consequences of anaphylaxis.
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<table>
<thead>
<tr>
<th>Effector mechanisms</th>
<th>Humans</th>
<th>Mice</th>
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<td><strong>Antibody isotypes</strong></td>
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| IgE                 | - Elevated IgE levels in individuals with allergic diseases[16, 19]  
- Purified IgE can transfer skin reactivity from a sensitized human subject to a naïve host[17, 21-23]  
- The anti-IgE Ab omalizumab can decrease the risks of anaphylaxis[50-55] | - PCA and PSA induced by transfer of antigen-specific IgE into naïve mice and challenge with the antigen[8, 25]  
- IgE-mediated PCA and PSA is abrogated in mice lacking the high affinity IgE receptor FceRI[15]  
- ASA partially reduced in IgE-deficient or FceRI+/- mice in some models, but not in others[33, 89, 93, 103, 192, 193] | |
| IgG                 | - No definitive evidence to date  
- Cases of anaphylaxis reported following treatment with therapeutic mAbs without detectable levels of anti-drug IgE[194-196]  
- Injection of low doses of C3a, C4a or C5a in the skin of healthy volunteers induces immediate wheal and flare reactions[66-69]  
- Blood levels of C3a, C4a and C5a correlate with the severity of anaphylaxis in humans[85] | - IgG1, IgG2a and IgG2b (but not IgG3) can induce PCA[50-50]  
- IgG-PSA is reduced in FcεRII/III-/- mice[51, 52]  
- IgG1- and IgG2b- (but not IgG2a-) PSA is enhanced in FcγRIIB/-/- mice[52]  
- Mice deficient in FcεRIII exhibit enhanced systemic anaphylaxis upon challenge with 2,4G2 anti-FcεRII/III Abs[20]  
- Mice deficient for IgG1 or FcγRIII are largely protected in several ASA models[89, 102, 103]  
- ‘Humanized’ mice expressing human FcεRI or FcγRIIA can develop IgG-mediated anaphylaxis[150, 151, 153] | |
| **Complement**      |        |      |
| Anaphylatoxins      | - Injection of low doses of C3a, C4a or C5a in the skin of healthy volunteers induces immediate wheal and flare reactions[66-69]  
- Blood levels of C3a, C4a and C5a correlate with the severity of anaphylaxis in humans[85] | - Reduced peanut-induced anaphylaxis in C4-/- mice[197]  
- Reduced IgE-PCA in mice in which mast cells lack C3aR or C5aR[198]  
- Anaphylaxis induced by direct activation of complement by peanut extract in one model[17]  
- C3-/- mice can fully develop IgG-PSA model[199]  
- ASA is not affected in C2-, C5- and C5aR-deficient mice, or after depletion of complement using cobra venom factor[92, 200] | |
| Mast cells          | - Elevated levels of tryptase have been detected during acute anaphylaxis in humans[69, 79-82]  
- High occurrence of anaphylaxis in patients with mastocytosis[85,87] | - IgE-PCA and PSA markedly reduced in various strains of mast cell-deficient mice[52, 88-89, 102, 120]  
- ASA reduced in mast cell-deficient mice in some studies, but not in others[51, 54, 89,93, 103, 192, 201] | |
| Basophils           | - No definitive evidence to date  
- “Basophil activation tests” used to diagnose or confirm allergen sensitization[96-99] | - Controversial: some reports indicate a contribution of basophils to IgG-PSA[52, 54, 56] or ASA[53, 89, 91], while others found no significant role for basophils[52, 92, 99, 202] | |
| Neutrophils         | - MPO levels are increased in patients with anaphylaxis as compared to healthy donors[106] | - Antibody-mediated neutrophil depletion reduces IgG-PSA and ASA in some[51, 53, 85], but not all[51, 103] models | |
| Monocytes/ macrophages | - Not yet determined | - Depletion of monocytes/macrophages using clodronate liposomes can reduce IgG-PSA and ASA[52, 89, 92, 102, 103] | |
| Platelets           | - No definitive evidence to date  
- Anaphylaxis in humans is associated with platelet activation[108] | - No definitive evidence to date  
- Depletion of platelets with anti-platelet antibodies (daily for 3 days) or neuraminidase does not reduce ASA[102] | |
| **Mediators**       |        |      |
| Histamine           | - Aerosol administration of histamine induces bronchoconstriction in healthy volunteers[114, 115]  
- Intravenous administration of histamine in volunteers can reproduce many of the symptoms of anaphylaxis[116, 117]  
- H1 antihistamines are commonly used as adjunctive therapy for acute anaphylaxis and anaphylactoid reactions[118] | - Histamine injection induces anaphylaxis[103, 204]  
- H1 antihistamine reduces IgE-PSA[203]  
- IgG-PSA and ASA are reduced in mice pre-treated with H1 antihistamine in some models[52, 101, 102], but not in others[53, 102]  
- Mice deficient for the histidine decarboxylase (HDC) gene are protected from IgE-PSA[203]  
- H1R- and H2R-deficient mice are partially protected from IgE-PSA[204] | |
| Cysteinyl leukotrienes (CysLTs) | - Levels of some CysLTs are increased during the onset of anaphylaxis[31-33]  
- Intradermal injection of leukotriene B4 (LTB4), LTC4 and LTD4 induces a wheal and flare reaction in healthy volunteers[134]  
- Aerosol administration of LTC4 and LTD4 in healthy subjects induces bronchoconstriction[134, 135] | - Reduced IgE-PSA in mice deficient for LTC4[135]  
- Mice deficient for CysLT1R also have significantly reduced IgE-PCA[136] |
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Table 1. Roles (or potential roles) of various antibodies, effector cells and mediators in anaphylaxis in humans and mice

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<table>
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<tr>
<td><strong>PAF</strong></td>
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<tr>
<td>- Injection of PAF in the skin of healthy volunteers induces wheal and flare reactions⁷⁻¹²⁵</td>
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<td>- Circulating PAF levels increase and circulating PAF-AH activity decreases in proportion to the severity of anaphylaxis⁶⁵, 82, 128</td>
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<tr>
<td>- PAF is released during IgG-PSA and ASA⁵³, ⁹¹</td>
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<tr>
<td>- Injection of PAF induces anaphylaxis²⁰⁶</td>
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<tr>
<td>- Reduced ASA in mice deficient for the PAF receptor (PAFR)²⁰⁷</td>
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<tr>
<td>- PAFR antagonists can partially reduce anaphylaxis in IgG-PSA and ASA models⁵², ⁵⁷, ⁵⁸, ⁹¹, ¹⁰², ¹⁰³</td>
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<tr>
<td><strong>Others</strong></td>
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<td>- Anaphylaxis induces increases in levels of many mediators which could potentially contribute (positively or negatively) to the clinical signs and symptoms. This includes various cytokines and chemokines, prostaglandins, tryptase, bradykinin, serotonin, etc.</td>
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<tr>
<td>- Mast cell-derived prostaglandin D₂ (PGD₂) can limit IgE-PCA and IgE-PSA¹⁸⁵</td>
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Table 2. Key concepts and therapeutic implications.

- Although mice clearly can develop both IgE- and IgG-dependent anaphylaxis, the existence of IgG-mediated anaphylaxis in humans has not been conclusively demonstrated.
- In addition to mast cells and basophils, macrophages, neutrophils, and perhaps other leukocytes, and platelets, also may produce a diverse array of inflammatory mediators during anaphylaxis, and such products have the potential to contribute to reactions that may be difficult to treat, protracted in nature, or biphasic.
- Genetic modifiers and other host factors, as well as gene-environment interactions, may influence the development of anaphylactic reactivity, as well as the presentation and/or severity of anaphylaxis.
- Although the potential evolutionary benefit of anaphylaxis remains uncertain, recent evidence in mice suggests that anaphylaxis may have effects that can reduce the toxic effects of certain arthropod or reptile venoms.
A. At low concentration of IgG Abs

- **Ab isotypes and FcRs**
  - IgE
  - FcεRI
  - Antigen

- **Effector cells**
  - Mast cells
  - Basophils

- **Potential mediators**
  - Histamine
  - CysLTs
  - Prostaglandins
  - Heparin
  - Proteases
  - Serotonin

B. At high concentration of antigen/IgG Abs

- **Ab isotypes and FcRs**
  - IgG
  - Activating FcγR

- **Effector cells**
  - Neutrophils
  - Monocytes/Macrophages

- **Potential mediators**
  - PAF
  - CysLTs

- **Various cytokines/chemokines**
- Nausea
- Vomiting
- Abdominal pain
- Diarrhea
- Flushing
- Urticaria
- Angioedema
- Itch
- Cough
- Wheeze
- Dyspnea
- Bronchoconstriction
- Hypoxia
- Hypotension
- Tachycardia
- Vasodilatation
- Vascular permeability
- Syncope
- Rhinorrhea
- Sneezing
- Angioedema
- Stridor
- Flushing
- Urticaria
- Angioedema
- Itch
- Cough
- Wheeze
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Histamine

Histamine
Histamine
Histamine
Histamine

Histamine
PAF
CysLTs

Histamine
Anaphylatoxins
PAF
CysLTs

Histamine
CysLTs
Cytokines/chemokines
bradykinin, tryptase, prostaglandins, heparin, etc…