Human IgE-independent systemic anaphylaxis

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Anaphylaxis is a rapidly developing, life-threatening, generalized or systemic allergic reaction that is classically elicited by antigen crosslinking of antigen-specific IgE bound to the high-affinity IgE receptor FcεRI on mast cells and basophils. This initiates signals that induce cellular degranulation with release and secretion of vasoactive mediators, enzymes, and cytokines. However, IgE-independent mechanisms of anaphylaxis have been clearly demonstrated in experimental animals. These include IgG-dependent anaphylaxis, which involves the triggering of mediator release by IgG/antigen complex crosslinking of FcγRs on macrophages, basophils, and neutrophils; anaphylaxis mediated by binding of the complement-derived peptides C3a and C5a to their receptors on mast cells, basophils, and other myeloid cells; and direct activation of mast cells by drugs that interact with receptors on these cells. Here we review the mechanisms involved in these IgE-independent forms of anaphylaxis and the clinical evidence for their human relevance. We conclude that this evidence supports the existence of all 3 IgE-independent mechanisms as important causes of human disease, although practical and ethical considerations preclude their demonstration to the degree of certainty possible with animal models. Furthermore, we cite evidence that different clinical situations can suggest different mechanisms as having a primal role in anaphylaxis and that IgE-dependent and distinct IgE-independent mechanisms can act together to increase anaphylaxis severity. As specific agents become available that can interfere with mechanisms involved in the different types of anaphylaxis, recognition of specific types of anaphylaxis is likely to become important for optimal prophylaxis and therapy. (J Allergy Clin Immunol 2016;137:1674-80.)

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Anaphylaxis is a rapidly developing, life-threatening, generalized or systemic allergic reaction.[1] Foods, drugs, and insect stings are the most common causes of this disorder.[2] Classically, anaphylaxis is induced by antigen crosslinking of antigen-specific IgE that has bound to the high-affinity IgE receptor (FcεRI) on mast cells and basophils.[3] Crosslinking of IgE and its receptor induces a signaling cascade that results in mast cell degranulation with release of mediators, including histamine, as well as preformed cytokines and proteases, and synthesis and secretion of additional cytokines, as well as lipid mediators, such as platelet-activating factor (PAF), leukotrienes, and prostaglandins.[4] Passive immunization studies in which mice were sensitized by injecting an antigen-specific IgE antibody, followed by enteral or parenteral exposure to that antigen, support the importance of IgE and mast cells in antigen-induced shock.[5] Indeed, both passive and active immunization studies in which mice were challenged orally with the appropriate antigen have generally demonstrated that genetic or antibody elimination of IgE, mast cells, or the IgE-binding chain of FcεRI (FcεRIα) completely suppresses anaphylaxis development.[6-8] In contrast, studies in which mice were actively immunized with an antigen, followed by parenteral challenge with the same antigen, have often revealed that anaphylaxis can occur in the absence of the classical IgE/FcεRI/mast cell pathway and demonstrated that a disorder that closely resembles IgE-mediated systemic anaphylaxis can be mediated by mechanisms that involve IgG rather than IgE.[9-11] Consistent with this, mice that are passively immunized with an IgG_1, IgG_{2a}, or IgG_{2b} (but not IgG_3) mAb specific for the hapten trinitrophenyl (TNP) have anaphylaxis, which is nearly indistinguishable clinically from IgE-mediated anaphylaxis, when challenged parenterally but not enterally with a TNP-protein conjugate.[5,6,8] These observations, coupled with several human clinical observations, suggest that IgE-independent anaphylaxis might be clinically important. Here we will first review observations that prove the existence of IgG-mediated anaphylaxis in mice and describe differences in the mechanisms behind the classical IgE-mediated pathway and the alternative IgG-mediated pathway in this species, as well as the clinical implications of these differences. Next, we will review observations that support the existence of IgG-mediated anaphylaxis in human subjects, as well as the implications and limitations of these observations. Finally, we will discuss the evidence and its limitations for other antibody-independent mechanisms of anaphylaxis in both mice and human subjects.

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Abbreviations used
NSAID: Nonsteroidal anti-inflammatory drug
PAF: Platelet-activating factor
TNP: Trinitrophenyl

MURINE EVIDENCE FOR IgG-MEDIATED ANAPHYLAXIS

Evidence for IgE-independent, IgG-dependent anaphylaxis was provided by studies in which mice were immunized and then parenterally challenged with a potent antigen.[11] In some of these active immunization models, disease developed even if mice were first treated with an anti-IgE mAb but was suppressed if mice were instead treated with the rat IgG_{2b} mAb 2.4G2. This mAb binds to and triggers but then blocks the inhibitory low-affinity IgG receptor FcγRIIB and the stimulatory low-affinity IgG receptor FcγRIII and indirectly blocks the other murine FcγRs, FcγRI and FcγRIV.[11,12] The existence of IgE-independent anaphylaxis in actively immunized mice was demonstrated most conclusively by studies that (1) induced severe anaphylaxis in actively immunized IgE- or FcγRIα–deficient mice but not in actively immunized mice that lacked all stimulatory FcRs (ie, FcRγ-deficient mice) and (2) demonstrated reduced severity or absence of anaphylaxis in actively immunized mice that lacked function of 1 or more of the stimulatory murine FcγRs.[11-14]

Subsequent passive immunization studies demonstrated that an anti-IgE mAb would block anaphylaxis when mice were sensitized with an antigen-specific IgE mAb but not when mice were sensitized with an antigen-specific IgG_1, IgG_{2a}, or IgG_{2b} mAb, whereas reciprocal results were found when passively immunized mice were treated with 2.4G2.[10-12,15,16] The severity of systemic anaphylaxis in these IgG passive immunization models was normal or increased in mice deficient in FcεRIα.[13] In contrast, anaphylaxis in mice passively sensitized with an antigen-specific IgG_1 mAb was totally absent in mice deficient in FcγRIII (the only stimulatory murine FcγR that binds mouse IgG_1), whereas total suppression of anaphylaxis in mice sensitized with an IgG_{2a} mAb (which binds to all 3 stimulatory murine FcγRs) required deletion or blocking of all of these receptors.[10,12] The importance of FcγRs in murine IgG-dependent anaphylaxis was also shown by the unique inability of IgG_3, among the murine IgG isotypes, to mediate anaphylaxis, which correlates with the observation that IgG_3 is the only murine IgG isotype that does not bind to any stimulatory murine FcγR.[17,18]

CLINICAL IMPLICATIONS OF STUDIES OF MURINE IgG-MEDIATED ANAPHYLAXIS

Studies of murine IgG-mediated anaphylaxis by several groups have evaluated the mediators involved, the responsible cell types, and the quantities of antigen required to induce shock. Nearly all studies have identified PAF, rather than histamine, as the mediator most important in IgG-mediated anaphylaxis in actively immunized mice,[11,19,20] although this has not been investigated thoroughly in passively immunized mice. In contrast to agreement about the importance of PAF in IgG-mediated anaphylaxis in actively immunized mice, different studies have identified monocytes/macrophages, basophils, or neutrophils as the critical cell type in IgG-mediated anaphylaxis.[11,19,20] All of these cell types express FcγRIII and FcγRIV in mice, and all are capable of producing PAF in response to appropriate stimuli.[18,20-24] Differences in cell types that appear to be responsible for IgG-mediated anaphylaxis can result from differences in mouse strains used, stimuli that elicit anaphylaxis, endogenous bacterial flora, and/or animal husbandry practices.

Results of studies that compared the doses of antigen required to induce IgE- versus IgG_1-mediated anaphylaxis suggest that the dose of challenge antigen determines when IgG-mediated anaphylaxis can occur. In mice that were passively sensitized with high-affinity IgE or IgG antibodies to TNP, 100- to 1000-fold less TNP-conjugated protein was required to induce shock in IgE- than in IgG-sensitized mice.[15] This was true regardless of the extent of TNP labeling of the TNP-conjugated protein, although less TNP conjugate was required to induce either IgE- or IgG-mediated anaphylaxis when the protein was heavily labeled.[15] These observations are consistent, respectively, with the much higher affinity of FcεRI than FcγRIII, the much higher ratio of cell-bound to serum IgE than IgG, and the better cross-linking of an antigen-specific mAb by an antigen that has multiple copies of the epitope bound by that mAb.

Because IgG-mediated anaphylaxis requires a much larger dose of antigen than IgE-mediated anaphylaxis, anaphylaxis induced by means of parenteral administration of a small quantity of antigen (eg, insect sting) is much more likely to be IgE mediated. Similarly, anaphylaxis induced by antigen ingestion (eg, food allergy) always appears to be IgE mediated[6,7] because induction of anaphylaxis in food allergy models requires systemic absorption of ingested antigen and only a very small percentage of ingested antigen is absorbed with all epitopes intact.[7,8] In contrast, both IgE- and IgG-mediated anaphylaxis can be induced by parenteral administration of a relatively large quantity of antigen (eg, infusion of a therapeutic antibody or drug),[15] particularly an antigen that has multiple iterations of an antibody-reactive epitope (eg, a carbohydrate antigen, such as dextran).

The difference in antigen dose requirement for IgE- versus IgG-mediated anaphylaxis allows IgG to act both as a mediator of anaphylaxis and a blocker of IgE-mediated anaphylaxis, depending on antibody and antigen concentrations (Fig 1). In the presence of antigen-specific IgE, antigen-specific IgG antibody will block anaphylaxis that would otherwise be induced by a low dose of antigen by intercepting antigen before it can bind to mast cell–associated IgE and by interacting with the inhibitory receptor FcγRIIB (Fig 1, *A* and *B*)[15,25] but mediate anaphylaxis induced by a higher antigen dose (Fig 1, *C* and *D*). The ability of IgG to both block antigen access to mast cell–associated IgE and to mediate anaphylaxis through IgG/antigen complex binding to stimulatory FcγRs can create the counterintuitive situation in which an intermediate dose of antigen will induce IgG- but not IgE-mediated anaphylaxis in the presence of both antigen-specific IgE and IgG (Fig 1, *C*).[15]

LIMITATIONS OF STUDIES OF MOUSE IgG-MEDIATED ANAPHYLAXIS

Although experimental evidence that IgG-mediated anaphylaxis can occur in mice is unequivocal, there are concerns about the interpretation of studies that identify the importance of different cells and receptors in this process. Nearly all studies