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Understanding the mechanisms of anaphylaxis

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Abstract

Purpose of review—The present review considers recent reports that identify the roles of key intermediate signaling components and mediators during and after mast cell activation and degranulation leading to anaphylaxis.

Recent findings—Mechanisms of anaphylaxis are becoming better understood as the interaction of several regulatory systems in the mast cell activation and degranulation signaling cascade. Multiple tyrosine kinases, activated after immunoglobulin E binding to the high-affinity receptors for immunoglobulin E (FcεRI), exert both positive and negative regulation on the signaling cascade, which may vary with genetic background or mutations in signaling proteins. Calcium influx, the essential, proximal intracellular event leading to mast cell degranulation, is controlled also by both negative and positive regulation through calcium channels. Sphingosine-1-phosphate is emerging as a newly realized mediator of anaphylaxis, acting as a signaling component within the mast cell and as a circulating mediator.

Summary—Anaphylaxis is a systemic reaction involving multiple organ systems, but it is believed that it may be influenced by cellular events in mast cells and basophils resulting in the release of mediators. Therefore, understanding the mechanisms of mast cell activation and degranulation is critical to understanding the mechanisms of anaphylaxis. Recent reports have identified important regulatory components of the signaling cascade and, consequently, potential targets for therapeutic intervention.

Keywords

allergic reaction; anaphylaxis; mast cells

Introduction

Anaphylaxis is a systemic reaction involving multiple organ systems. It is most frequently associated with exposure to allergens and the release of mediators from mast cells and basophils. Anaphylaxis may potentially lead to death, although this is not the usual outcome. The sudden and often unanticipated onset and the catastrophic physiological impact of anaphylaxis make proper diagnosis and appropriate treatment critical to beneficial outcomes. Since the first description of anaphylaxis by Portier and Richet [1] over a century ago, anaphylaxis has been recognized as both a dangerous and a puzzling disease. No less confounding has been the absence of consensus on definitions and diagnostic criteria, and clear insight into underlying pathophysiologic mechanisms. Recent reports have addressed these issues by proposing diagnostic criteria, identifying key chemical mediators, and identifying key intermediates contributing to mast cell and basophil activation.

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Progress in defining anaphylaxis

With the initiative of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network, representatives from several organizations in the United States and abroad met in symposia in 2004 and 2005 to debate and seek consensus on a universally accepted definition and clinical criteria for identification of anaphylaxis. The outcomes of these symposia were published in two reports in the *Journal of Allergy and Clinical Immunology* [2,3]. In seeking a definition both useful and accessible to the lay public, the participants proposed simply that, 'Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.' Even more significant for emergency response and treatment, the participants established a set of three diagnostic criteria for anaphylaxis to include observations of skin and mucosal tissue symptoms, respiratory distress, reduced blood pressure, and/or gastrointestinal symptoms over a time course of minutes to hours after exposure to allergen [2,3].

Lack of a consensus definition and the use of various criteria for diagnosis have made estimating the incidence and prevalence of anaphylaxis difficult. A review of major epidemiological studies of anaphylaxis [4], conducted by the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group in 2004, estimated that the frequency of anaphylaxis was 50–2000 episodes per 100,000 persons or a lifetime prevalence of 0.05–2.0%. The working group acknowledged that because of underdiagnosis and underreporting this estimate is probably not representative of the true incidence and prevalence of anaphylaxis. Differing study methodologies, nonrepresentative or small sample size, differing geographical locations and environmental conditions, inconsistent identification and classification of cause, and incomplete data collection contribute to problems for study conduct [5•]. Adoption of the consensus definition and diagnostic criteria for anaphylaxis should help establish standardized reporting and aid future epidemiological studies.

Events in anaphylaxis

Anaphylaxis, for the most part, is believed to arise from the activation of mast cells and basophils through a mechanism generally understood to involve crosslinking of immunoglobulin (Ig) E and aggregation of the high-affinity receptors for IgE, FcεRI. Upon activation, mast cells and/or basophils quickly release preformed mediators from secretory granules that include histamine, tryptase, carboxypeptidase A, and proteoglycans. Downstream activation of phopholipase A2 (PLA2), followed by cyclooxygenases and lipoxygenases, produces arachidonic acid metabolites, including prostaglandins, leukotrienes, and platelet activating factor (PAF). The inflammatory cytokine, tumor necrosis factor-α (TNF-α) is released as a preformed mediator, and also as a late-phase mediator with other cytokines and chemokines. Many of these mediators are believed responsible for the pathophysiology of anaphylaxis. Histamine stimulates vasodilation, and increases vascular permeability, heart rate, cardiac contraction, and glandular secretion. Prostaglandin D2 is a bronchoconstrictor, pulmonary and coronary vasoconstrictor, and a peripheral vasodilator. Leukotrienes produce bronchoconstriction, increase vascular permeability, and promote airway remodeling. PAF is also a potent bronchoconstrictor and increases vascular permeability. TNF-α activates neutrophils, recruits other effector cells, and enhances chemokine synthesis [6]. These overlapping and synergistic physiological effects contribute to the overall pathophysiology of anaphylaxis that variably presents with generalized urticaria and angioedema, bronchospasm, and other respiratory symptoms, hypotension, syncope, and other cardiovascular symptoms, and nausea, cramping, and other gastrointestinal symptoms. Biphasic or protracted anaphylaxis may occur.

There are reports of anaphylaxis in humans occurring independently of IgE, and alternative mechanisms have been suggested including complement anaphylatoxin activation, neuropeptide release, immune complex generation, cytotoxicity, T-cell activation, or even multiple mechanisms [7••]. An alternative mechanism for anaphylaxis has been described recently in mouse models, in which two mechanisms of anaphylaxis have been demonstrated – one pathway involving IgE, the crosslinking of FcεRI receptors, mast cell degranulation, and the release of histamine and PAF; and another pathway involving IgG, the IgG receptor, FcγRIII, and the release of PAF, not histamine, as the major mediator [8–11,12•]. Mouse models for studying mast cell activation and degranulation and anaphylaxis offer the opportunity to study knockout models to discern the contribution of specific genes to overall signal transduction pathways. Most human cases of anaphylaxis are seen to be IgE-mediated, but there is some evidence to support IgG-mediated and nonimmunologic origins, often distinguished as 'anaphylactoid' [12•]. The mechanisms for IgG-mediated anaphylaxis in humans are neither well documented nor well understood [13].

The most frequently identified triggers for anaphylaxis include foods (especially peanuts and tree nuts), drugs (antibiotics, vaccines, medications, and anesthetics), insect venoms, latex, and allergen immunotherapy injections [3,14]. There is also a significant number of anaphylaxis cases reported for which there is no cause identified (idiopathic anaphylaxis) [15,16].

Mechanisms for anaphylaxis

Signaling pathways for activation of mast cells have been studied *in vitro* using mast cells from humans and other mammals, and *in vivo* in tissues and whole animal models. Studies reported in the last year have highlighted the role of the regulation of mast cell activation in the progression to anaphylaxis. Critical to understanding the mechanisms of anaphylaxis is understanding the regulation of intracellular events that result in the release of anaphylaxis mediators. The activation of intracellular signaling cascades results in rapid degranulation of mast cells, the generation of arachidonic acid metabolites (lipid mediators), and later production of cytokines and chemokines. The mechanisms for mast cell activation and mediator release are dependent on the binding of IgE to FcεRI. Upon antigen binding to IgE, these receptors aggregate and initiate the signaling cascade. Components of FcεRI have specific sequences, the immunoreceptor tyrosine-based activation motifs (ITAMs), containing tyrosine residues that are phosphorylated by Src family member tyrosine kinases, including Lyn and Syk, activated after receptor aggregation. Phosphorylated ITAMs serve as high-affinity docking sites for Src homology (SH2) domain-containing proteins, including Lyn and Syk. Syk is recruited to the signal complex and is activated further by tyrosine autophosphorylation and phosphorylation by Lyn. These activated tyrosine kinases phosphorylate the transmembrane adaptor molecules linker for activation of T cells (LAT) and non-T-cell activation linker (NTAL), which provide scaffolds for direct or indirect interactions for additional adaptor molecules including Grb2, Gads, Shc, and SLP76, the guanine nucleotide exchange factors and adaptor molecules Sos and Vav, and the major signaling enzymes phospholipase Cγ (PLCγ) and PI3 kinase (PI3K). Activation of PLCγ and PI3K releases calcium from intracellular stores and activates protein kinase C (PKC), leading to mast cell degranulation. Through Sos and Vav, the Ras–Raf–mitogen-activated protein (MAP) kinase cascade is also activated leading to PLA2 activation, arachidonic acid metabolism, and the production of lipid mediator generation and release; and the activation of the transcription factors, AP-1, nuclear factor of activated T cells (NFAT) and NF-κB leading to cytokine and chemokine production. The tyrosine kinase Fyn also acts through another signaling cascade to phosphorylate the adaptor protein Gab2 and activate PI3K, Bruton's tyrosine kinase (Btk), PLCγ, and sphingosine kinase and the generation of sphingosine-1-phosphate (S1P) [17,18].

Reports over the last year have highlighted further the key role for the tyrosine kinases involved in the initial stages of FcεRI activation, as well as downstream regulation of the signal complex. There is both positive and negative regulation of many of the components in the signaling cascades. Lyn, Syk, and Fyn are considered key components of the signal transduction cascade, but other tyrosine kinases have been identified recently that also play a role, such as Hck, which was reported in knockout mice in 2007 to exert a positive regulation of mast cell degranulation by inhibition of Lyn and by phosphorylation of FcεRI [19]. The tyrosine kinase, Lyn, is involved in initial tyrosine phosphorylation to launch the signal cascade, and it also recruits adaptor proteins that regulate downstream events [17]. Intensity of stimulation of FcεRI was seen to be a determinant of downstream signaling component regulation through the activation of Lyn. Low-intensity stimulation (monomeric IgE, IgE in the presence of anti-IgE, or IgE and low-antigen) positively regulated mast cell degranulation and cytokine production by inhibiting Lyn activity and its association with FcεRI. In contrast, high-intensity stimulation (high-IgE and high-antigen) negatively regulated mast cell activation through enhanced Lyn activity, association with FcεRI, and increased Syk activation [20]. The multiple roles of Lyn in the regulation of mast cell activation also may be evident in the different phenotypes that have been reported recently for Lyn knockout mice and mast cells, exhibiting enhanced, diminished or similar allergic reactions when compared with wild-type [17]. It now appears from data presented in a recent report that genetic variation may account for some of these differences. When wild-type and Lyn-deficient mice from two different genetic backgrounds, 129/Sv and C57BL/6, were compared, investigators observed significant differences in mast cell responsiveness. Wild-type 129/Sv mice were more susceptible to anaphylaxis than the C57BL/6, and bone-marrow-derived mast cells (BMMCs) from 129/Sv mice showed faster, enhanced degranulation when activated. In addition, BMMCs from 129/Sv Lyn(-/-) showed enhanced degranulation, whereas the C57BL/6 Lyn(-/-) BMMCs showed a significantly diminished response. C57BL/6 Lyn(-/-) BMMCs also had reduced expression of Fyn, and silencing Fyn expression in human mast cells reduced degranulation [21•]. In another recent study, a strain of mice that are epilepsy-resistent, but anaphylaxis-prone, was shown to be deficient in the expression of Lyn. A related variant of epilepsy-prone mice are anaphylaxis-resistant. BMMCs cultured from the anaphylaxis-sensitive mice showed reduced Lyn and Syk activity and degranulation, consistent with a phenotype for Lyn(-/-) BMMCs, whereas the anaphylaxis-resistant mice exhibited a phenotype similar to BMMCs cultured from wild-type mice. Also, BMMCs from the anaphylaxis-sensitive mice, similar to the Lyn (-/-) BMMCs, have reduced Syk activity, prolonged activation of Erk and JNK, enhanced activation of Akt, and increased Fyn activity. It was proposed in 2007 that the impaired function of Lyn, a negative regulator of mast cell activation, was responsible for the susceptibility of these mice to anaphylaxis [22]. These recent studies highlight the effects of genetic background and variability on mast cell degranulation and anaphylactic responses, and the critical role of the tyrosine kinases Lyn and Fyn in negative and positive regulation of the mast cell signaling cascade.

Activated Fyn constitutes a second, tyrosine kinase-mediated pathway leading to mast cell degranulation. In addition to the negative and positive roles played by Lyn in regulating immediate as well as downstream events in mast cell signaling, Fyn has been shown to be required for degranulation and cytokine production [23]. Fyn phosphorylates the adaptor molecule, Gab2, leading to the assembly of a signal complex through the recruitment of PI3K, PLCγ, Btk, and Vav [17]. There are also recent reports of regulation of PI3K and consequent inhibition of anaphylactic responses. In 2008, a member of the regulator of G protein signaling (RGS) family, RGS13, was shown to inhibit PI3K signaling by binding to the p85 regulatory subunit and blocking the interaction with the scaffolding proteins Gab2 and Grb2. RGS13 (-/-) mice exhibited enhanced mast cell degranulation and anaphylaxis [24••].

PI3K signals have been reported also to be negatively regulated through the activity of the phosphatase SH2-containing inositol phosphatase 1 (SHIP1), which dephosphorylates phosphatidylinositol-3,4,5-trisphospate (PIP_3) generated by the action of PI3K on its substrate PIP_2. In the last year, several reports have identified new mechanisms for the regulation of PI3K. Novel activators of SHIP1 inhibited the PI3K-mediated phosphorylation of downstream substrates Akt, p38, and Erk, and when administered *in vivo* to mice prevented acute cutaneous anaphylaxis [25]. An IgG–IgE fusion protein acting through the inhibitory receptor FcγRIIB inhibited Syk and Erk1/2 phosphorylation, mast cell degranulation, and anaphylaxis through the activation of SHIP1 and SHP-1/2 phosphatases [26]. RasGRP1 is now also identified as an important regulator of FcεRI-mediated PI3K signaling. RasGRP1(-/-) mice were resistant to anaphylaxis, releasing much less histamine than wild-type controls. RasGRP1(-/-) derived BMMCs exhibited impaired degranulation, reduced cytokine transcription and secretion, and decreased RhoA, PI3K, Akt, and PKC activation [27]. The Rac-binding protein, SWAP-70, is also an apparent regulator of the PI3K pathway in mast cells. SWAP-70(-/-) mice were resistant to anaphylaxis, and PI3K and Akt activity are also decreased in SWAP(-/-) BMMC [28]. These recent reports identify the contribution of the Fyn–Gab2–PI3K signaling pathway that is essential to mast cell degranulation and anaphylaxis.

The tyrosine kinase, Fyn, also plays a role in the generation of S1P, an emerging mediator of anaphylaxis. It was determined recently that two isoforms of sphingosine kinase (SphK1, SphK2) expressed in BMMCs are activated by Fyn after FcεRI aggregation. The two isoforms exhibit differing degrees of dependence on signaling components downstream from Fyn, including Gab2 and PI3K [29]. Activated SphK2 produces S1P, triggers calcium influx, activates PKC, and stimulates cytokine production and mast cell degranulation. S1P was shown to contribute to anaphylaxis in an autocrine/paracrine mechanism arising from both mast cell degranulation stimulated by SphK2 activity in mast cells and circulating S1P generated from SphK1 activity from other sources, possibly endothelial cells or platelets activated by the release of PAF [30••,31,32].

Regulation of calcium concentration plays a central role in mast cell degranulation, and several calcium channels now appear to contribute to maintaining the threshold of degranulation through negative and positive regulation. Reports published in the last year have highlighted the key role of the regulation of calcium influx for mast cell activation. The calcium-activated nonselective cation channel, transient receptor potential melastatin 4 (TRPM4), exerted a negative regulation of calcium influx, and TRPM4-deficient mice displayed increased mast cell degranulation and mediator release and more sensitivity to anaphylaxis [33•]. Positive regulation of calcium concentration was observed in the store-operated channels stromal interacting protein 1 (STIM1) and calcium release-activated calcium channel modulator 1 (CRACM1). STIM1 or CRACM1 deficiency impaired mast cell degranulation, production of cytokines, and immediate-type allergic reactions *in vivo*, including defective anaphylactic responses in knockout mice [34•,35•]. Store-operated calcium channels in mast cells are reported to be negatively regulated by stimulation of the A2b adenosine receptor resulting in decreased calcium influx and mast cell degranulation. A2b receptor-deficient BMMCs showed increased degranulation, calcium influx and cytokine release and A2b(-/-) mice were more sensitive to anaphylaxis [36].

Released mediators

Although S1P appears as a newly recognized mediator of anaphylaxis, histamine, tryptase, leukotrienes, prostaglandins, TNF-α, and PAF, generated by mast cell or basophil activation, have been long shown to trigger the major physiological manifestations of anaphylaxis [6]. Nitric oxide, generated by activation of nitric oxide synthase (NOS), acts as a potent vasodilator through the stimulation of guanylyl cyclase, subsequent generation of cGMP, and relaxation

of vascular smooth muscle. Nitric oxide can be increased by the action of circulating histamine, leukotrienes, TNF-α, and PAF on the endothelium and can exert pronounced effects on the vasculature sufficient to induce anaphylactic hypotension [37]. Working in a mouse model, investigators reported recently that PAF-mediated anaphylaxis was dependent on PI3K, Akt, endothelial NOS, and nitric oxide, but independent of inducible NOS and guanylyl cyclase [38]. In another recent study, the NOS inhibitor *N*(G)-nitro-L-arginine methyl ester (L-NAME), but not guanylyl cyclase inhibitors, attenuated antigen-induced anaphylaxis in mice, confirming a nonguanylyl cyclase pathway arising from NOS activation [39]. PAF concentration also was shown to be an important determinant of the severity of anaphylaxis in a recent report of human studies that evaluated the severity of reaction concentrations of PAF, and PAF acetylhydrolase, an inactivating enzyme for PAF. Serum PAF levels were higher for anaphylaxis patients than for controls and correlated with the severity of anaphylaxis. Also, there were inverse correlations between serum concentrations of PAF and PAF acetylhydrolase, between PAF acetylhydrolase and severity of anaphylaxis, and between PAF acetylhydolase and fatal anaphylaxis [40•]. The strong correlation data suggest inclusion of PAF with histamine, tryptase, and other mast cell released mediators in a possible biomarker panel for anaphylaxis susceptibility [41].

Mutations in signaling components

The complex regulation of mast cell signaling unfolding in these recent studies highlights the sensitivity of the system to dysregulation arising from a single component. This is evident in the many studies of mouse models in which a single protein has been knocked out, or with different genetic backgrounds, resulting in either resistance or sensitivity to anaphylaxis. In human mast cells, the influence of a single mutation can be seen in the expression of the D816V activating mutation in the tyrosine kinase KIT, leading to mast cell proliferation and mastocytosis [42]. Mast cell proliferation and the prevalence of episodes of hypotension in mastocytosis patients prompted studies that identified associations between systemic mastocytosis and anaphylaxis [43,44,45•,46]. The activating D816V KIT mutation also was recently reported in some mastocytosis patients with recurrent unexplained anaphylaxis [45•]. In another report, omalizumab was shown to be effective for the treatment of anaphylaxis in two systemic mastocytosis patients [47]. The association of the activating KIT mutation with mastocytosis and anaphylaxis offers the possibility that the presence of additional genetic polymorphisms or mutations in mast cell signaling components may contribute to dysregulation and a predisposition to anaphylaxis [48].

Conclusion

The adoption of a consensus definition and diagnostic criteria is a significant step in improving the identification and treatment of anaphylaxis and will contribute to improved estimates of occurrence. A better understanding of the mechanisms of anaphylaxis is beginning to unfold through the examination of mast cell signaling. With the identification of signal intermediates and emerging mediators, such as S1P, new potential targets for therapeutic intervention are coming to light. The discovery of mutations that influence the regulation of mast cell signaling may prove useful in identifying individuals susceptible to anaphylaxis. Understanding the mechanisms of anaphylaxis offers potential therapeutics for the prophylactic or emergency treatment of this life-threatening condition.

Acknowledgements

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 363–364).

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