

Pathophysiology of Immunologic and Nonimmunologic Systemic Reactions Including Anaphylaxis



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KEYWORDS

- Anaphylaxis • Anaphylactic reaction • Anaphylaxis mechanism of production
- Anaphylaxis mediators

KEY POINTS

- Anaphylaxis is more a syndrome than a specific condition.
- Episodes may be immunologically or nonimmunologically induced.
- There are numerous pathophysiologic pathways that can participate in the production of anaphylactic episodes.

INTRODUCTION

Anaphylaxis is an acute and potentially life-threatening systemic reaction that occurs rapidly on the introduction of a given trigger. But what causes anaphylaxis? Classically, the term anaphylaxis was used to describe an allergen-driven process in which particular IgE antibodies were induced on exposure to an antigen, causing mast cell (MC) activation via cross-linking of IgE receptors. The centralized role of the MC in anaphylactic events has been well known for decades. And it is the activation of the MC that leads to the degranulation of its many diverse mediators including histamine, PAF-1, prostaglandins, leukotrienes, and tryptase, to name a few. These mediators induce the typical clinical signs associated with anaphylaxis including bronchoconstriction, vasodilation, and hypovolemia. The potential result of this constellation of systemic manifestations could be fatal by cardiac failure and/or asphyxiation.^{1,2}

Over time, however, it has become clear that non-IgE-mediated pathways exist in relation to MC activation and that these pathways can lead to the same clinical symptoms defined by classic anaphylaxis. To offer a clear view into the many pathways and

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interwoven mechanisms involved in anaphylactic events, it will be helpful to distinguish the MC as the chief effector cell. The mechanisms involved in MC activation can then be divided into immunologic and nonimmunologic mechanisms, as seen in **Fig. 1**. The immunologic mechanisms include the classic IgE-mediated pathway as well as an IgG-mediated pathway. The nonimmunologic mechanisms include direct MC activation via a multitude of receptors including PAF and opioid receptors.³ Also of note is the human G-protein-coupled receptor, MRGPRX2, found on MC that has been found to be a receptor for certain drugs and cationic proteins that can cause direct MC degranulation and subsequent anaphylactic events.¹

Finally, there is the non-MCcell-mediated mechanism causing anaphylactic episodes. An example being over sulfate chondroitin sulfate contamination of heparin which results in identical clinical symptoms associated with anaphylaxis by direct activation of the contact system and/or complement with likely no involvement of MCs.¹ It is these varying pathways and mechanisms that we will further explore in the discussion later in discussion.

HISTORY/BACKGROUND

Anaphylaxis is an intriguing phenomenon in that many could recognize its presentation, especially when its occurrence is rapid and dramatic, whereas also being difficult to clearly define when pressed. Therefore, we feel it important to trace the term anaphylaxis back to its origins and follow the ever-evolving criteria needed to establish its diagnosis today. The term "anaphylaxis" was first established by Charles Richet and Paul Portier in 1901 when attempts were made to induce prophylaxis to the venom of a sea anemone but inadvertently invoked the opposite reaction. There initial goal was to inoculate or immunize certain animals to the venom of the sea anemone species but in fact the animals were acquiring an increased sensitivity to the venom.

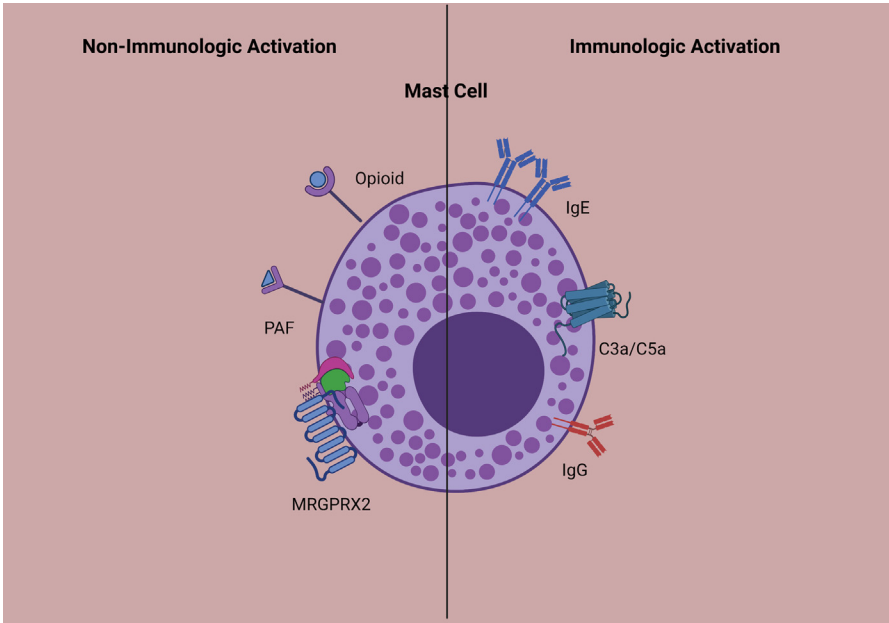


Fig. 1. Mast cell. (Created with [BioRender.com](#)).

They noted that on the readministration of the venom the animal subjects would often experience fatal reactions, reactions that appeared systematically different from the venom administered at lethal doses. And from this realization came the term "anaphylaxis" ("ana" being Greek for "opposite," "phylaxis" being Greek for "protection").^{1,4,5}

By 1925, the term anaphylaxis was becoming more widespread in the clinical setting though it was still unclear whether humans could be grouped with the animal models whereby anaphylactic sensitization had been seen. Within the next 20 years, the use of medications was becoming more common and with that, it had become apparent that humans were indeed subject to experiencing anaphylactic reactions. And in 1945, anaphylaxis was formally defined for the first time by Robert Cooke in his classic text "Allergy in Theory and Practice" as "a special or particular immunologic type of induced protein (or hapten) sensitivity and may in for experimental animals and may properly be considered as a subdivision of allergy."^{4,6,7} It is also interesting to highlight that during this time the relationship of anaphylaxis with the MC was not yet known.

The MC was first discovered by Paul Ehrlich in 1877. However, the MC's function remained a mystery for the better part of a century until 1952 when J. F. Riley and G. B. West uncovered the fact that a significant source of histamine came from the MC. And thus, the connection was established between the MC and anaphylaxis.

As time passed, we saw the advent of polypharmacy and with it an increased prevalence in anaphylactic events. It was not long after the discovery of immunoglobulin E (IgE) that a clear mechanism of anaphylaxis came into view and that was by the way of IgE activation of MCs via cross-linking of IgE receptors residing on MCs and basophils. But in keeping with the evolution of anaphylaxis as a term, more and more endotypes surfaced which only deepened the complexity involved with distinguishing a set criterion for anaphylaxis. By the 1970s, the updated definition of anaphylaxis was "a systemic, immediate hypersensitivity reaction caused by IgE-mediated immunologic release of mediators from MCs and basophils." But the recognition that different endotypes exist beyond the IgE-mediated mechanism borne a new term, anaphylactoid reaction. "The term 'anaphylactoid reaction' refers to a clinically similar event not mediated by IgE."⁸⁻¹¹

Objections arose to this distinction in 2003 when the World Allergy Organization suggested that all events, whether IgE-mediated or not, should be labeled as "anaphylactic episodes." It was also proposed to further classify the mechanism of production of these episodes into immunologic and nonimmunologic. The nonimmunologic events would be synonymous with the term "anaphylactoid" and the immunologic events were further categorized into IgE-mediated and non-IgE mediated.⁹

This now leads us to the most current definition of anaphylaxis which is a modification of the WAO definition: "Anaphylaxis is a potentially serious, systemic reaction, either immunologic or nonimmunologic, that is usually rapid in onset, of variable severity, and may cause death. Severe anaphylaxis is characterized by either compromise of breathing and/or circulation and most often is preceded by milder signs/symptoms and occasionally occurs without such symptoms."¹²

DISCUSSION

To fully understand the intricacies and interwoven mechanisms that propagate an anaphylactic event let us first begin with the principal effector cell, the MC. It is important to point out that there has been multiple effector cells identified in relation to the different mechanisms of anaphylaxis though the MC has been studied the most extensively and is intimately related to the IgE-mediated mechanism. MCs are now considered to be highly versatile immune cells involved with many physiologic and

pathologic states. MCs function as immunomodulators and in homeostatic processes in the epithelium, endothelium, and nervous system. Over time it has also become more apparent that the way in which MCs mature and function has a direct correlation with the microenvironment they inhabit. These local microenvironments impact the way MCs react to various stimuli through the release of a range of biologically active mediators. Their dispersal into a vast array of different tissues allows MCs to participate in many biological processes such as angiogenesis and tissue repair as well as involvement in innate and adaptive immunity.⁴ But whereby do MCs originate? And how do they arrive at their varied destinations?

There has been much debate on the origin of the MC with some earlier studies pointing to the liver and yolk sac as sites of embryonic MC origin, but there was simply no way to distinguish between MC precursors and pluripotent stem cells. We now know, due to the work of Kitamura and colleagues, that human MCs are derived from a common pluripotent hematopoietic progenitor originating in the bone marrow. But unlike other cells of hematopoietic origin, which mature in the bone marrow before being released into circulation, MCs travel as immature progenitor cells through the circulation to designated tissues whereby they complete their maturation process.^{1,4}

The mechanisms involved in the recruitment of progenitor MCs to peripheral tissues during physiologic and inflammatory states have not been completely revealed. Several studies from the past decade highlight the importance of some integrins, adhesion molecules, chemokines, and their receptors, as well as cytokines and growth factors as important players in the directed migration of MCs to specific locations under normal and pathologic circumstances. They tend to settle in areas found at the border between the host and the external environment. These sites have the highest entry potential of pathogens or contact with harmful substances and include the skin, respiratory mucosa, and gastrointestinal tract. These microenvirons foster phenotypic changes which effect function, contents, structure, and the response to endogenous stimuli and drugs.⁴

The capacity of MCs to promptly interact with the microenvironment and respond through the release of an array of biologically active mediators is in a delicate balance, whereby the insufficient regulation of MC functions can lead to distressing effects. Because of this, MCs have been implicated in the pathogenesis of several chronic allergic/inflammatory disorders, as well as acute events such as anaphylaxis. The mechanisms by which MCs, as well as the other effector cells that will be addressed, mediate an anaphylactic event can be further categorized into immunologic and nonimmunologic.^{1,4}

Immunologic Mechanisms

IgE-mediated pathway

The first immunologic pathway that we will discuss is the classic IgE-mediated pathway. As previously stated, the chief effector cell in this pathway is the MC. And to a lesser extent the basophil can participate. This pathway is characterized by the formation of allergen-specific IgE and subsequent binding of this IgE to the FcεRI receptor primarily on MCs. After re-exposure to the allergen, there is a cross-linking of IgE/FcεRI complexes, as seen in [Fig. 2](#).¹³ The formation of these complexes leads to a dimerization of the receptor. Downstream signaling activates a series of tyrosine kinases which then phosphorylate tyrosine residues in the intracellular portion of the IgE receptor. After this, a second protein kinase comes to further phosphorylate the chain. This action triggers a sequence leading to the activation of Inositol triphosphate (IP3) which results in an influx of extracellular calcium

IgE Cross-linking Induces Mast Cell Activation and Degranulation

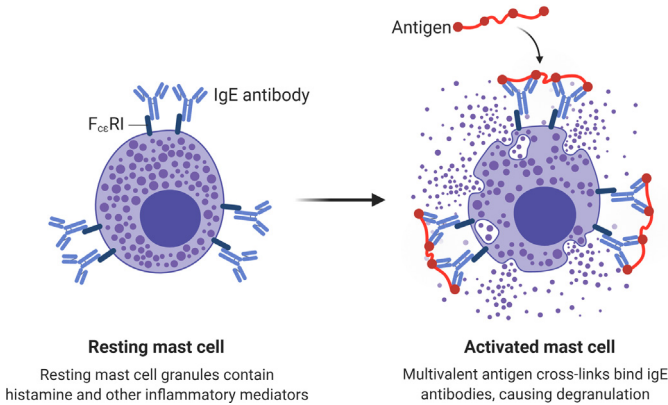


Fig. 2. Mast cell activation and degranulation. (Reprinted from "IgE Cross-linking Induces Mast Cell Activation and Degranulation" by BioRender.com (2021)).

into the cell.¹ Granules containing preformed mediators such as histamine, tryptase, and PAF are then released from the cells, whereas the de novo synthesis of other inflammatory mediators such as leukotrienes, prostaglandins, and cytokines occurs as well. The result is the smooth muscle contraction and increased vascular permeability associated with anaphylaxis.¹³

The importance of this process was illustrated decades ago, when it was determined that purified IgE was capable of transferring skin reactivity from sensitized human subjects to naive hosts.^{14–17} Similarly, transfer of antigen-specific IgE into naive mice sensitizes the animals to have anaphylaxis on subsequent exposure to that allergen.^{18,19} Such IgE-mediated anaphylaxis is absent in mice that lack the high-affinity IgE receptor $Fc\epsilon RI$, as well as in MC-deficient mice, further signifying the importance of IgE-mediated MC activation in such models of anaphylaxis.^{20–23}

IgG-mediated pathway

Until recently, only the IgE-mediated pathway had been universally accepted as the mechanistic explanation of anaphylaxis induction. But there is now more and more evidence emerging in line with the possibility that human MC activation via $Fc\gamma RI$ -IgG can produce anaphylactic events. Both animal models and human observational studies point to the fact that IgG alone or in immune complexes (ICs) can activate MCs and either initiate or contribute to the severity of anaphylactic reactions.² IgG antibodies recognize and bind to Fc gamma receptors ($Fc\gamma Rs$), which have different affinities and are expressed on multiple cell types.^{2,24,25} Among the many receptor types involved with activation signaling, $Fc\gamma RI$ is the only one that binds with high affinity to monomeric IgG, primarily IgG1 and IgG3. It is expressed on both MCs and neutrophils. $Fc\gamma RI$ binding to specific IgG1 can lead to activation of MCs.^{2,24–30} Both IgG1 and IgG3 can instead activate $Fc\gamma RI$ expressed on monocytes and macrophages. Although $Fc\gamma RI$ receptors are normally occupied by monomeric IgG, this does not prevent their activation by IgG ICs. The latter has higher binding affinity and can therefore displace monomeric IgG and trigger hypersensitivity responses. In mouse models, it has been shown that antigens can induce macrophages, basophils, and neutrophils to release PAF by activating $Fc\gamma RIII$ or $Fc\gamma RIV$.^{31,32} With these models, IgG seemed

to require higher levels of specific IgG antibodies and antigens, in contrast to IgE-mediated anaphylaxis, which can be seen in Fig. 3. This is likely due to the lower affinity of FcγRs compared with FcεRI.

Another good example of the IgG–neutrophil/macrophage-mediated pathway comes from a multicenter prospective study conducted on 86 patients who experienced anaphylaxis to an NBMA received during anesthesia. There were 86 matched controls.³³ NMBA is a low-molecular-weight antigen that is administered via IV in rather large quantities which favors IC formation and circulation. In this study, 31% of patients with anaphylaxis had no biomarkers of IgE–dependent anaphylaxis. These data validate the notion that an alternative pathway independent of IgE exists in patients who experienced anaphylactic events to NMBA. The research also showed that the more severe the reaction, the higher the concentration of anti-NMBA IgG, aPAF, neutrophil activation markers, as well as markers for FCyR activation. It was also revealed that neutrophils became increasingly more activated and underwent the release of neutrophil elastase and developed elevated neutrophil extracellular traps. This occurred soon after anaphylaxis onset, particularly in patients without any evidence of IgE-dependent anaphylaxis. This demonstrates the importance of this pathway separate from the classic IgE mediated pathway. Ultimately this study shows it is possible that an IgG-mediated pathway could compound the severity of an anaphylactic event coupled with the activation of the IgE pathway and induce anaphylaxis in the absence of IgE.^{2,33}

Complement activation

The final pathway belonging to the immunologic mechanism of anaphylaxis is complement activation. The initiation of the complement cascade occurs via a multitude of stimuli and results in the formation of C3a, C4a, C5a. These mediators are referred to as anaphylatoxins.^{1,34} Several sources of evidence have highlighted the production of C3a, C5a as well the depletion of complement levels in human anaphylaxis. This suggests that these anaphylatoxins can be involved in anaphylaxis.^{1,35–37}

On complement activation, C3a, C5a are released which subsequently triggers the activation of MCs, basophils, endothelial cells, and smooth muscles via their particular

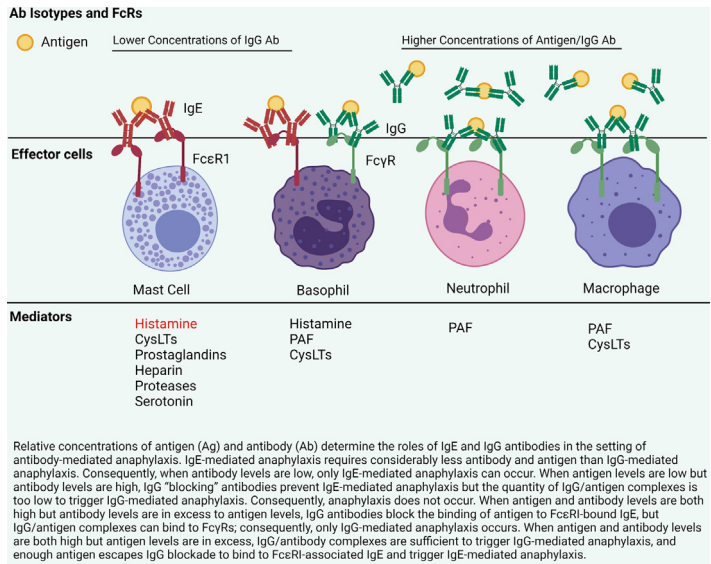


Fig. 3. IgE versus IgG mediated activation. (Created with BioRender.com).

receptors. It has been shown that C3a has a direct effect on MC activation in rat, human MC line HMC-1, and in CD34-derived human MCs.^{38,39} These potent inflammatory mediators have also been shown to directly induce vascular permeability and smooth muscle contraction. The phenotypic response elicited from an IgE-mediated reaction can be indistinguishable from that produced by complement activation. But complement induced events may differ from IgE reactions in that they can present on the initial exposure.²

ICs have been shown to activate the complement system, generating anaphylatoxins such as C3a that can then further activate MCs and basophils.⁴⁰ There are also instances whereby complement activation occurs independently from IC formation. An example of this has occurred in reactions to drugs solubilized in therapeutic liposomes and lipid-based excipients like the diluents used for preparations of propofol and paclitaxel. Cremophor EL, the diluent previously used, was able to activate complement under physiologic conditions, forming large micelles with serum lipids and cholesterol.^{41–43}

Another example of complement activation producing anaphylactic reactions has been seen in events to dextran and von Willebrand factor (vWF).^{44,45} Keeping in line with some of the hallmark features of complement reactions, they can occur on the first infusion and can be prevented by pretreatment with antihistamines, steroids, and NSAIDs.

Dextran is a polysaccharide with a repetitive structure that can be immunogenic. In a small subpopulation of individuals with high titers of preformed dextran-reactive antibodies (DRAs) of IgG class, the infusion of dextran generates harmful ICs. They activate complement and cause the aggregation of leukocytes and platelets. The aggregated material is sequestered in the lung, and the release of vasoactive mediators leads to signs and symptoms associated with anaphylaxis.⁴⁴

In a clinical prospective study, a patient with severe von Willebrand disease was found to have IgG alloantibodies against vWF along with a history of posttransfusion anaphylaxis. During an 18-day period, the patient was treated with factor VIII-vWF concentrate and with recombinant factor VIII. Complement system activation and plasma levels of antibodies to vWF and complement-fixing IgG-vWF complexes were evaluated. IgE, IgA, and IgM antibodies to vWF were not found.⁴⁵ During this study the patient experienced symptoms of anaphylaxis when IgG antibodies to vWF were measured at days 1 and 6 after replacement with factor VIII-vWF concentrate. This observation suggested a cause-effect relationship between the formation of IgG-vWF complexes and massive complement activation in posttransfusion non-IgE-mediated anaphylactic reactions to vWF.⁴⁵ In this patient, there was no indication of MC activation or the contact phase of the coagulation cascade. Therefore, it was concluded that the clinical syndrome was a direct effect of complement anaphylatoxins on vascular permeability and smooth muscle contraction.^{2,46}

Nonimmunologic Mechanisms

There are several agents capable of inciting MC degranulation by directly binding to cell surface receptors.^{1,13} Such agents include neuropeptides such as substance P (SP), certain polycationic molecules, stem cell factor, cytokines, opioids, and several different drugs. It has also been found that physical factors such as heat, cold, or exercise can incite MC degranulation though the mechanisms underlying these events are less clear.^{1,13,47}

It is, however, the more recent discovery of the MRGPRB2 receptor found on mice MCs that has garnered much attention.^{1,13} This mouse MC receptor was determined to be the ortholog of human MRGPRX2 via reverse-transcriptase in mouse peritoneal

MCs. Both MRGPRB2 and MRGPRX2 share similar characteristics. They reside on, MCtc, and respond to similar ligands. Analyses conducted by McNeil et al. revealed that certain drugs containing structural patterns called tetrahydroisoquinoline (THIQ) were capable of activating MRGPRB2. These structural patterns are present on certain drugs such as icatibant, several fluoroquinolones, and neuromuscular blocking drugs (NMBDs). Drugs within these classes can promote Ca^{2+} mobilization in HEK293 cells that express the MRGPRX2 receptor thereby stimulating MC degranulation and inducing the release of histamine, TNF, and PD2, which is illustrated in Fig. 4.⁴⁸ It is interesting to note that whereby these ortholog receptors differ is in the concentration of agonist required for activation. Studies have suggested that the differences in the amino acid sequences of MRGPRX2 and MrgprB2 influence the ability of peptide ligands to activate these receptors.^{49,50}

The range of drugs known to induce MRGPRX2-dependent MC pathway is continuing to expand. For instance, in mouse models, passive cutaneous anaphylaxis was induced with iodinated contrast, and a clear association with MCs and MRGPRB2 was found. However, capacity for receptor-induced activation by these peptidergic drugs does not fully account for the unpredictable severity of reactions. It is becoming clearer that distinct receptor levels, as well as the overall functionality of the receptor may be the key to gaining further insight into the different reactions of certain individuals than others.⁵¹ Evidence is accumulating to support the notion that genetic alterations to the MRGPRX2 protein do influence the response of the receptor to identifiable triggers. A specific example includes the results of Reddy and colleagues in which a single amino-acid changed the induction of pruritis through its receptor.⁵² Other studies have been investigating the role of MRGPRX2 variants in relation to patients with drug reactions, specifically in regards to the activity of the receptor. Though some of these studies are still ongoing, the specific role of different mutations in regards to clinical epidemiology is yet to be fully understood.⁵³

Non-mast Cell-mediated Mechanisms

In addition to these mast-cell-derived mediators of anaphylaxis, there exist other systems of inflammation that can be activated to produce mediators that cause the same signs and symptoms associated with classic anaphylaxis. These systems include coagulation, complement, kallikrein, and platelet-related pathways. It is also important to realize that though these pathways can lead to an anaphylactic event in the absence of MC involvement, MC activation can also recruit and activate these same pathways leading to a synergistic escalation in the clinical features associated with anaphylaxis.^{1,13}

The hallmark example of a non-MC cell-mediated mechanism is the over-sulfated chondroitin sulfate (OSCS) contaminated unfractionated heparin. A brief background will be offered to help explain how these mechanisms were discovered. In January 2008, health authorities in the United States began receiving reports of groups of acute hypersensitivity reactions in patients undergoing dialysis that had been occurring since November 2007. The symptoms associated with these reactions included hypotension, facial swelling, tachycardia, urticaria, and nausea. Though initial investigations yielded no obvious answer, an investigation conducted by the CDC revealed a common thread to these reactions; heparin sodium used for injection. Once this link was established the contaminant was then identified to be OSCS. Though the culprit was made known, a biological link between OSCS and adverse clinical events remained elusive.⁵⁴

But then a study was conducted by Kishimoto and colleagues to attempt to determine this missing biological connection. And their results revealed that OSCS found in

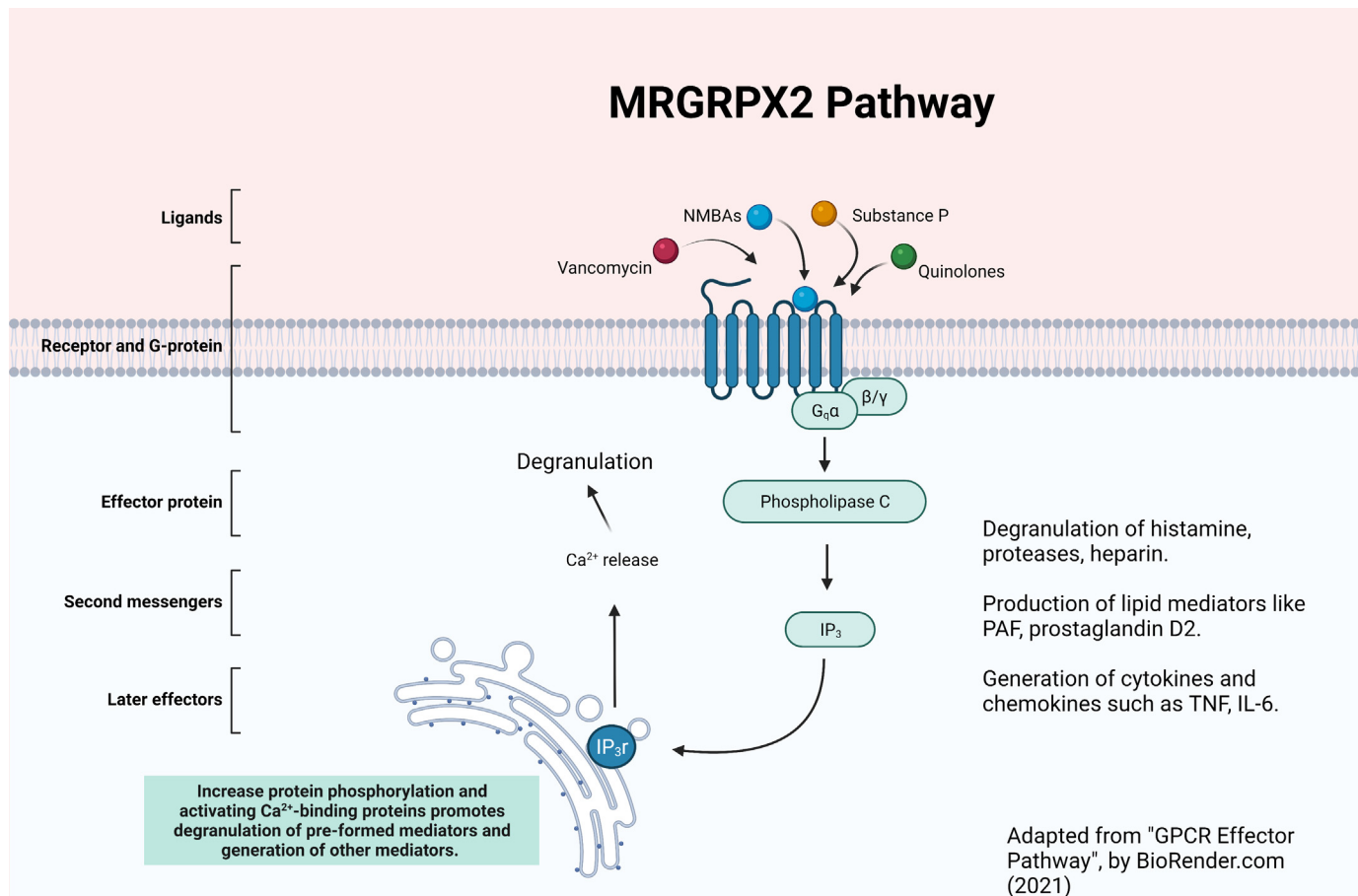


Fig. 4. MGRPX2 pathway. (Adapted from "GPCR Effector Pathway", by BioRender.com (2021)).

contaminated lots of unfractionated heparin, as well as a synthetically generated OSCS reference standard, directly activated the kinin–kallikrein pathway in human plasma. The activation of which can lead to the generation of bradykinin, a potent vasoactive mediator. They also discovered that OSCS induced generation of C3a and C5a, potent anaphylatoxins derived from complement proteins. Activation of these 2 pathways was unexpectedly linked and dependent on fluid-phase activation of factor XII.⁵⁴

Other Recruited Pathways

We will next touch on the different pathways that can be recruited during anaphylaxis. MCs have several mediators responsible for activating these pathways, including the aforementioned kallikrein–kinin system, complement, and the clotting cascade.

In relation to anaphylaxis, activation of the kallikrein–kinin contact system occurs after MC degranulation has been stimulated via allergen/IgE complex. As previously stated, this initiates the release of several preformed mediators as well as the de novo synthesis of others including leukotrienes, histamine, tryptase, carboxypeptidase A, and proteoglycans. Heparin, with its components of highly sulfated polysaccharide, provides the negatively charged surface required for the binding of plasma protease factor XII on its release from MCs. This binding induces a conformational change in zymogen FXII. Activated FXII (FXIIa) activates plasma kallikrein (PK) zymogen to the active protease, which, in turn, proteolytically generates the peptide hormone bradykinin from its precursor, high-molecular-weight kininogen (HK). Bradykinin then acts on the G protein-coupled bradykinin B2 receptors (B2Rs) to increase vascular permeability.⁵⁵

There has also been evidence to support the involvement of the clotting cascade in more severe episodes of anaphylaxis. Although most evidence illustrating the link between anaphylaxis and DIC has largely come from animal trials there have been a few case reports establishing this same connection. In these cases, it was reported that the patients were typically in sustained periods of anaphylactic shock and subsequently developed worsening hypotension, thrombocytopenia, prolonged PT/aPTT, and decreased fibrinogen. An investigation then ensued to determine a connection between DIC and anaphylaxis. Choi and colleagues discovered that PAF is a major influence in the developing DIC in the setting of anaphylaxis. Active systemic anaphylaxis was induced in mouse models with the subsequent development of DIC. The development of DIC manifestations was then found to be prevented in the models that were pretreated with PAF-antagonist. Furthermore, manifestations of DIC were seen in models that received an injection bolus of PAF.⁵⁶

Mediators

Several mediators have been identified over the years in relation to anaphylactic events. Histamine has long been considered the pivotal player and has been shown to induce all of the hallmark symptoms associated with anaphylaxis. Studies have shown that when administered via aerosol form or intravenously, histamine can cause bronchoconstriction, cutaneous flushing, and headaches as well as hypotension, tachycardia, an increased left ventricular function.^{57,58} Histamine is primarily contained within MCs and basophils and when released will bind to one of the 4 known receptors, labeled H1–H4. Studies have shown that the more systemic effects of histamine, such as tachycardia and bronchoconstriction, occur via the H1 receptor.^{57,58} Platelet-activating factor is another mediator whose role in anaphylaxis has been under more recent review. PAF is a very potent phospholipid-derived mediator that can activate a variety of cells expressing the PAF-receptor (PAF-R).^{59,60} These

Table 1
Mast cell mediators and their pathophysiologic activities

Mediators	Pathophysiologic Activities	Clinical Manifestations	Comments
Histamine	Contraction of smooth muscle, vasodilatation, increased vascular permeability, mucus secretion, and activation of nociceptive neuronal receptors	Wheezing, flushing, urticaria, pruritus, rhinorrhea, abdominal pain, diarrhea, and angioedema	Works through both H1 and H2 receptors. Although accounting for a large portion of the clinical manifestations, blockade of its activity does not control all manifestations completely
Prostaglandin	Smooth muscle spasm, affects platelet adherence, and vasodilatation	Wheezing, diarrhea, cramping abdominal pain, and hypotension	
Leukotriene	Smooth muscle contraction, increased vasopermeability	Probable main effect is wheezing with bronchoconstriction, possible hypotension	
Platelet Activating Factor	Activation of platelets, vasodilatation	May contribute to intravascular coagulation with platelet activation, probable hypotension, and shock	Levels have been directly correlated with the severity of events and fatalities, also levels of platelet-activating hydrolase, the enzyme responsible for its degradation, have been inversely correlated with severity and fatalities as well
Interleukins	Not well defined	Not well defined	In spite of lack of knowledge of exact effects, levels of some interleukins have been associated with the severity of episodes
Chymase	Possibly recruits complement by cleaving C3, may have a beneficial effect by inactivation of neuropeptides, can recruit contact system	Not well defined	Levels have been associated with direct activation of the contact system and thus indirectly associated with the severity of events

(continued on next page)

Table 1 (continued)			
Mediators	Pathophysiologic Activities	Clinical Manifestations	Comments
Tryptase	Not well defined	Not well defined	Used as a biomarker to diagnose events
Tumor Necrosis Factor	Not well defined	Not well defined	Levels have been associated with severity of events
Neuropeptides	Not well defined	Not well defined	Can magnify events by further degranulating mast cells
Recruited Pathways	Activation of the coagulation pathway has been associated with decreased Factor V, decreased Factor VIII, and decreased fibrinogen. Activation of complement cascade has been demonstrated by decreased levels of complement components 3 and 4 as well as the formation of C3a. Activation of the contact system has been demonstrated by the formation of kallikrein C1 inhibitor complexes as well as elevated levels of kinins.	Disseminated intravascular coagulation and hypotension	Levels of activation have been shown to correlate with the severity of episodes

From Lieberman P, Garvey LH. Mast Cells and Anaphylaxis. Curr Allergy Asthma Rep. 2016 Mar;16(3):20; with permission.

include endothelium, smooth muscle, and MCs.^{61,62} PAF is very similar to histamine in their physiologic effects. It can induce vascular permeability, decrease cardiac output, induce smooth muscle contraction of the central airways and gastrointestinal tract, and lead to vasodilation with consequent circulatory collapse.^{2,63,64} PAF is inactivated by PAF acetylhydrolase (PAF-AH) and has a half-life of 3 to 13 minutes. In relation to anaphylaxis, PAF induces a potent mediator in anaphylaxis pathogenesis such as PGE₂, as well as nitric oxide.^{64,65} MC-derived PAFs appear to be important in IgE-mediated reactions in humans as demonstrated by the severe anaphylaxis in patients with high levels of PAF and decreased PAF-AH activity, with the lowest levels of PAF-AH activity being associated with a 27-fold higher risk of severe or fatal anaphylaxis compared with the risk in patients with normal levels of PAF-AH activity.^{66,67}

Other important mediators include CysLTs, tryptase, prostaglandins, and various cytokines/chemokines (IL-2, IL-6, IL-10, TNF) whose pathophysiologic activity and clinical manifestations can be found detailed in [Table 1](#). Of note, it has been described by Brown and colleagues that these cytokines mentioned have been associated with severe anaphylactic reactions.⁶⁸

SUMMARY

Anaphylaxis remains one of the most urgent medical emergencies, in which immediate recognition and prompt intervention can be the difference between life and death. Our understanding of the antibodies, effector cells, and mediators that contribute to the manifestations seen in anaphylaxis has continued to evolve and progress. Despite the knowledge gained in these mechanisms, the clinical management of anaphylaxis has remained the same for years. As we've discussed, most of the anaphylactic events are due to systemic MC degranulation. This degranulation process was initially thought to be primarily IgE-mediated. But over time it has become more apparent that a significant number of anaphylactic events occur by multiple different mechanisms either synergistically or independently. An example includes the discovery of the IgG-mediated pathway in inducing MC degranulation. There is also direct MC degranulation independent of IgE via PAF and opioid receptors as well as the human G-protein-coupled receptor, MRGPRX2, that has been found to be the receptor for many drugs and cationic proteins capable of producing direct MC degranulation and anaphylactic events. Our hope is that as we continue to advance in our understanding of the pathophysiology of anaphylaxis in all of its interconnected mechanisms, greater efforts to develop more effective approaches for preventing anaphylactic events as well as provide more effective options for prompt diagnosing and effective treatment will become more available.

CLINICS CARE POINTS

- Understanding of the complexities of anaphylaxis will result in better diagnosis with biomarkers, improved avoidance or pretreatment strategies, and more effective, individualized therapies.
- The remarkable efficacy of IM epinephrine enables effective therapy of anaphylaxis, regardless of pathways responsible.

DISCLOSURE

Sanofi (Consultant).

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