

What is anaphylaxis?

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Purpose of review

In the century since the discovery of anaphylaxis, research has yet to identify the mechanisms that cause a localized allergic response to become rapidly generalized, and particularly why only some sensitized individuals develop the clinical reaction on exposure. The possible components and steps in the process (proven and hypothetical) are reviewed with respect to their variation and regulation and their potential for therapeutic intervention.

Recent findings

Studies of insect sting allergy have revealed some of the gaps in our understanding, the relatively poor predictive value of our diagnostic tests, and more recently the early evidence for 'priming' of basophils and mast cells as a precursor or predictor of clinical reactivity. Recent literature has elucidated some of the products and regulatory pathways of the cells involved in the initiation of the anaphylactic response, the role of neurologic pathways, and the possible 'on-off switches' at the level of the immunoglobulin E receptors and their related signaling pathways.

Summary

This review incorporates old and new observations that may be related to the puzzling characteristics of anaphylaxis. Recognizing the gaps in our understanding helps to identify many areas that require further study and presents promising targets for future treatment and prevention of anaphylaxis.

Keywords

allergic reaction, anaphylaxis, insect allergy

Introduction

Anaphylaxis is underrecognized, underreported, undertreated and poorly understood [1–3]. This is a very surprising statement over 100 years after the first description of anaphylaxis, given that progress in our knowledge of immunology has permitted remarkable advances in diagnosis and treatment of other allergic conditions. The epidemiology of anaphylaxis has been described in very few published reports [4–11]. There are about 100 000 episodes each year in the USA, of which two-thirds are new cases, and almost 1% are fatal. Some have estimated that 10–20% of the US population is at risk for anaphylaxis by virtue of past history or existing sensitization [7]. Although most cases can be traced to specific trigger factors, some 20% or more are designated as idiopathic [8–12]. Even the treatment of anaphylaxis is controversial. Although epinephrine has long been held to be the treatment of choice, it is clearly underutilized and not always effective, whereas steroids are widely used despite the total lack of evidence to support this practice [1,13–14]. There is an obvious problem in conducting a placebo-controlled trial of any treatment for an acute life-threatening reaction like anaphylaxis, so some of these questions may be impossible to answer, at least in humans.

The history of anaphylaxis leads us to recognize the questions that need to be answered. When originally described by Portier and Richet in 1902 [15], anaphylaxis was a 'black box' in that there was no understanding at all of what mechanisms intervened between the allergen entering the body and the occurrence of the anaphylactic reaction [15]. In recent years, animal models have given us useful insights into some of the molecular mechanisms of anaphylaxis [16]. Although we now understand the existence of immunoglobulin E (IgE) molecules and receptors, many of the regulatory pathways upstream and downstream of IgE, and the action of many mediators, anaphylaxis still remains a black box. The more we study anaphylaxis the more we realize that the mechanisms of anaphylaxis still evade us. The simple triggering of mediator release from sensitized basophils and mast cells does not distinguish anaphylaxis from much simpler allergic responses such as sneezing, itchy eyes or wheezing. Portier and Richet would turn in their graves to know that we are little more enlightened than a century ago on the real nature of anaphylaxis. Our studies of insect sting anaphylaxis have made us acutely aware of our lack of understanding of anaphylaxis, and we will use this model to illustrate this sorry state of affairs.

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Abbreviations

CNS central nervous system
Ig immunoglobulin

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Are there markers for the diagnosis and prediction of anaphylaxis?

Recognition of our lack of understanding led to two expert workshops on anaphylaxis supported by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network, with the initial goal of arriving at a clinically useful definition of anaphylaxis. This seemingly simple task required over 30 h of wrangling during 4 days of enlightened discussion by the world's experts, and resulted in two published reports [2,17^{*}]. Aside from the definition of the acute clinical presentation of anaphylaxis, the workshops identified the areas most in need of research. 'An important immunologic feature of allergy is that not all sensitized subjects exhibit clinical reactivity. The exact series of events between contact with an allergen by a sensitized individual, and sufficient activation of mast cells, basophils and possibly other cells to induce an anaphylactic reaction, remains to be elucidated' [2]. 'The variable clinical nature of the anaphylactic response, even in the same individual, indicates that there is still much we do not understand. In the laboratory we need to identify biomarkers that accurately predict who is at risk to develop anaphylaxis and who has actually experienced an anaphylactic reaction' [2].

The dilemmas being recognized today first came to the attention of our group during our controlled trial of venom immunotherapy to prevent anaphylaxis in insect sting-allergic patients. Although all the patients had a history of sting anaphylaxis and had positive venom skin tests, 40% did not react to a live sting challenge [18]. This observation has been confirmed in many published studies. In a review of 11 such studies, we found that of 1195 such patients who were subsequently stung, 46% had systemic reaction. In our subsequent epidemiologic studies, we found that the frequency of venom sensitization in adults was eight times higher than the frequency of systemic reactions to stings [19,20]. Studies of insect sting allergy have also identified many sensitized individuals who get severe local allergic swelling to stings but rarely develop anaphylaxis [21–23].

These observations lead to the same major questions identified by the expert panels and workshops. Of primary interest is the simple question of 'why do some people react and other people don't, particularly when they seem to have the same venom-specific IgE?' There are several related questions. Are there measurable markers of anaphylaxis that correlate with the severity and pattern of the clinical response? Are there laboratory markers that distinguish the sensitized individuals who will react to a sting from those who will not? What is the mechanism that can, in the space of minutes, amplify a local allergic response into a global systemic reaction?

Insect sting allergy as a model of anaphylaxis

To begin to address these questions we undertook a sting challenge study over 10 years ago. We confirmed that only 30–40% of patients who were selected (by self-selection and by exclusion of very severe reactors) for this study had systemic reactions to a challenge sting [24,25]. We also confirmed previous reports that of the individuals who did not react to the first sting challenge, 20% reacted to a later sting [26,27]. Of special interest was our finding that less than 1% of the stings caused a reaction more severe than the patient's previous reactions. The risk of progressively worse reactions, therefore, seems to be much less common than generally believed. This is in contrast to the situation with peanut, where affected children often develop more severe reactions with subsequent exposure.

In the course of our sting challenge studies, we also noted surprising variability of venom skin test responses, such that a skin test could be positive at one point in time and negative at another for no apparent reason. We have confirmed this observation in our ongoing study of venom immunotherapy for prevention of large local sting reactions, and it has been reported recently in the literature [28,29]. This would also seem to be different from peanut as well as inhalant allergens, which have not been reported to show short-term variability in skin test responses. It is not yet clear whether this reaction is related to the technique (intradermal rather than puncture) or whether it has simply not been looked for with other allergens. Venom allergy differs in another interesting respect from peanut. Since venom immunotherapy is so safe and effective despite the anaphylactic nature of the condition, there is no apparent explanation for the observation that peanut immunotherapy was neither safe nor reliably effective [30].

Predicting the risk of anaphylaxis

In evaluating the risk of a reaction, we must consider both the chance of any reaction (frequency), and the chance of a severe reaction (severity). Skin test sensitivity seems to predict the frequency of a reaction, but not the severity of reaction [24,25,31]. In our study, the chance of a systemic reaction was significantly higher in individuals with a more severe history of previous reactions, those with a positive skin test at the time of the sting and those with a history of allergic rhinitis [25]. There was no relation of reactions to total serum IgE but a weak correlation existed with the presence of IgE to inhalant allergens. Age and the time since the last sting reaction were not factors. Laboratory studies showed a significantly higher chance of reaction when the baseline level of β -tryptase in the serum was elevated, and when there was a greater basophil release of histamine or leukotriene C4 (LTC4) in response to venom or histamine-releasing factor.

These findings suggest a higher level of basophil activation (or priming) in those who react to a sting. We found other suggestions of a priming effect in that the chance of a reaction to a challenge sting was greater when there had been a sting in the previous 3 months or when the patient had venom skin tests in the previous 4 weeks [27]. Venom exposure may increase the level of basophil responsiveness for a period of time. The association with allergic rhinitis may have a similar explanation: exposure to pollen in the preceding weeks may increase the activation status of basophils. My colleagues have previously reported [32] that circulating basophils show increased expression of activation markers after each nasal challenge. We plan studies to evaluate the predictive value of in-vitro measures of basophil priming in relation to sting challenge. Even this observation leaves open the question of what regulatory processes, extracellular and intracellular, determine the degree of basophil responsiveness. The concept of abnormal basophil releasability has been a focus of investigations by my colleagues at Johns Hopkins for decades [33–35]. The underlying mechanisms are within our reach.

This returns us to the fundamental question: why do some people react and others with the same allergy do not? Specific scenarios are especially puzzling.

- (1) Patients with previous systemic reactions do not react to every subsequent sting.
- (2) Patients with previous large local reactions have a very low risk of systemic reaction. (What prevents them from having anaphylaxis?)
- (3) Those with positive skin tests but no prior history of reaction may ultimately develop overt sting allergy. (What makes them become clinically reactive at some point in time?)

The large-scale GALEN project has also considered this question of why some sensitized individuals do not react to allergen exposure, and a list of possible determining factors was published [36**] (Table 1).

Table 1 Factors responsible for differences between asymptomatic individuals and patients presenting an immunoglobulin E (IgE) sensitization to allergens

Family history of atopy
Mono and polysensitization against allergens (high versus low responders)
Levels of allergen-specific IgE
Qualitative differences in allergen-specific IgE
Allergen molecules with high and low allergenic activity
Levels of allergen-specific IgG and IgA
Levels of total IgE
T-cell regulation
Polymorphism of the FcεRI
Negative signals in cells bearing FcεRI
Impact of bacterial superantigens

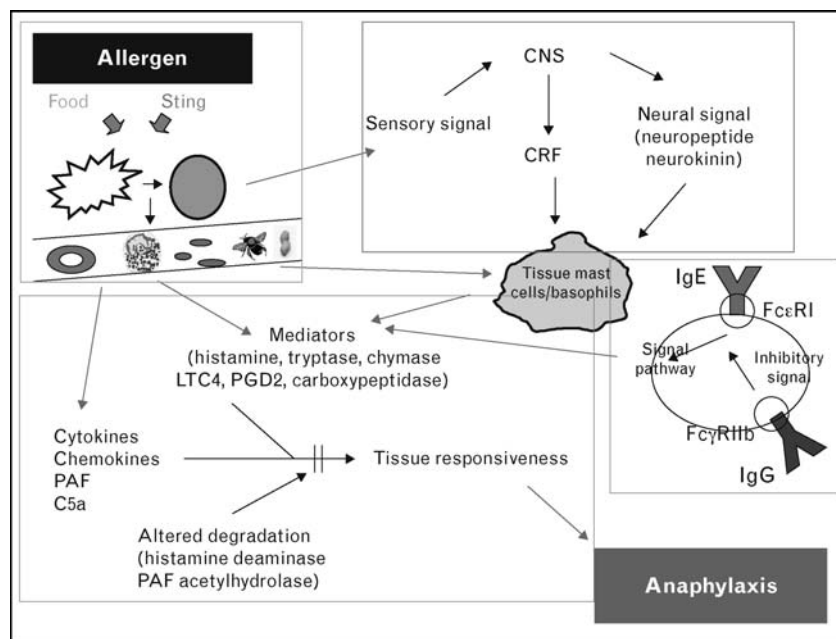
A GA²LEN project. Adapted from [36**].

Initial allergen effects after exposure

To further consider this problem, we must return to the 'black box' that was anaphylaxis in the time of Portier and Richet. Using the advances of the past few decades, I have tried to fill in the black box with many potential mechanistic pathways that may affect the clinical reaction to allergen (Fig. 1). We will consider each of the components of this figure, our current knowledge, and the needs for future research. The portal of entry itself may affect the type of response to the allergen. Allergen then binds to IgE which exists not only on tissue mast cells but also on dendritic cells which may influence the immunologic response, and potentially the degree of basophil priming (through production of interferon- α which regulates basophil interleukin-13 production) [37]. Allergen is then assumed to enter the circulation, although the quantity and time course of allergen circulation have never been demonstrated. An alternative hypothesis would be that some intermediate 'messenger' enters the circulation, perhaps deriving from mast cells or dendritic cells. The generalized manifestations of anaphylaxis may be related to basophil mediators released within the circulation, or to mediators released by tissue mast cells in response to other circulating factors (including allergen).

Central nervous system pathways in anaphylaxis

The potential involvement of neural pathways has been largely overlooked. The afferent limb may involve sensory signals from nerves exposed to allergen or to local mast cell products, but it is also possible that circulating factors directly affect the central nervous system (CNS). The efferent limb could cause release of neuropeptides and neurokinins that affect mast cell and other immune cell responses. There is a body of literature over four decades that demonstrates the potential for the CNS to regulate immune and anaphylactic responses. One interesting aspect is the conditioning of immune responses. In classical experiments published in *Science* 25 years ago, Ader and Cohen [38] described the ability to condition the immunosuppressive effects of cyclophosphamide treatment in a murine model of systemic lupus erythematosus. After conditioning the mice by giving saccharin prior to each dose of the drug, the immunosuppressive response could be elicited just by giving the saccharin! In other studies, antibody responses could also be conditioned [39]. Similarly, by administering saccharin prior to each time that anaphylaxis was induced by a sensitizing allergen, the anaphylactic response could ultimately be elicited just by the saccharin [40]. Further studies on this 'learned histamine release' were published in *Science* almost 25 years ago [41]. A final and impressive piece of evidence for a role of the CNS in anaphylaxis is the observation from more than 40 years ago that hypothalamic lesions in rats could ablate the anaphylactic response

Figure 1 Pathways that contribute to variability in the expression of anaphylaxis

Areas of potential variability that could impact the clinical response include the route of exposure; local effects on tissue mast cells and dendritic cells; local factors or allergen entering the circulation; central nervous system (CNS) pathways; basophil and mast cell receptors, signaling, and inhibitory pathways; mediator activity and tissue responsiveness. CRF, corticotropin-releasing factor; Ig, immunoglobulin; LTC₄, leukotriene C₄; PAF, platelet-activating factor; PGD₂, prostaglandin D₂.

[42]. Similarly, CNS lesions induced in the hypothalamus were shown to modulate guinea pig lung anaphylaxis [43]. There is obviously a potential role in anaphylaxis for hypothalamic processes which could include stress and endocrine factors. These would represent potential targets for treatment to prevent anaphylaxis in susceptible individuals. We may also wonder whether it would be possible to condition patients against anaphylaxis, analogous to behavior modification therapy. There is a clear need for research on CNS pathways in anaphylaxis.

Regulation of signaling pathways in anaphylaxis

Another area of great interest is the structure and function of the IgE receptor on basophils and mast cells, and the intracellular pathways that affect the ability of IgE activation to cause mediator release. The receptor itself may have altered structure or configuration that would render the individual more or less likely to develop allergic reactions (particularly the β -subunit necessary for signal transduction). As pointed out by my colleague Don MacGlashan [44], the intracellular signaling pathways are very complex and 'exquisite sensitivity is possible because there are multiple amplification steps in the signaling transduction reaction'. There are numerous potential abnormalities in these pathways that could affect the degranulation of the cell. One of the inhibitory pathways that has been of recent interest is the effect of

IgG binding to FCγRIIb receptors [45*,46]. The inhibitory signal that blocks normal IgE receptor signaling is mediated by SH2-containing inositol phosphatase (SHIP). This is one example of a pathway that may influence the clinical response to allergen and may be amenable to pharmacologic intervention [46–48]. A similar inhibitory pathway is mediated through the gp49B receptor [49]. Another signaling pathway that affects allergic reactions involves Syk protein, and may also be open to therapeutic intervention [50]. Other pathways have been investigated in animal models, including the role of interleukin (IL)-4, IL-9, IL-12 and generation of nitric oxide [51–54].

Mediator activity in anaphylaxis

Once there has been release of mediators from mast cells and basophils, there are potential abnormalities of the degradation pathways that could lead to increased chance or severity of reaction. There have been preliminary observations reported on such abnormalities of histamine deaminase, platelet-activating factor acetylhydrolase and carboxypeptidase metabolism [55–57]. Another interesting aspect of these mediators is the possibility that different mediators are released in different reactions, either in relation to the specific patient, the portal of entry, or the specific allergen. There is a poor correlation of serum tryptase and plasma histamine during acute allergic reactions, and neither correlated very well with

most of the manifestations of anaphylaxis [58]. There is a need to evaluate the relative quantity and time course of a wide range of mediators in relation to the causes and manifestations of anaphylaxis.

Conclusion

This effort to open up the 'black box' of anaphylaxis is critical to our efforts to understand this condition and to enable more accurate diagnosis, treatment and prevention. If we only understand what turns on the anaphylactic response (beyond the allergen and IgE), we would be one large step closer to being able to turn off the risk of anaphylaxis. Animal models can provide insights that may steer our studies of human anaphylaxis [16]. The model of insect sting anaphylaxis has been most revealing of the clinical and immunologic questions that remain unanswered, and should be equally useful in our investigation of these important problems. We have the ability to compare serum factors, cellular responses, genetic regulation and environmental influences in patients who do or do not react to challenge sting, in large local and systemic reactors, and in untreated and venom immunotherapy treated patients. Portier and Richet would be pleased with the prospects for the next century, and would hope that it does not take that long to unravel the mysteries of anaphylaxis.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 361–362).

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