Mechanisms of Anaphylaxis Beyond IgE

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Abstract

Anaphylaxis is an acute, life-threatening, multisystem syndrome resulting from the sudden release of mediators derived from mast cells and basophils. Food allergens are the main triggers of anaphylaxis, accounting for 33%-56% of all cases and up to 81% of cases of anaphylaxis in children. Human anaphylaxis is generally thought to be mediated by IgE, with mast cells and basophils as key players, although alternative mechanisms have been proposed. Neutrophils and macrophages have also been implicated in anaphylactic reactions, as have IgG-dependent, complement, and contact system activation. Not all allergic reactions are anaphylactic, and the presence of the so-called accompanying factors (cofactors or augmenting factors) may explain why some conditions lead to anaphylaxis, while in other cases the allergen elicits a milder reaction or is even tolerated. In the presence of these factors, allergic reactions may be induced at lower doses of allergen or become more severe. Cofactors are reported to be relevant in up to 30% of anaphylactic episodes. Nonsteroidal anti-inflammatory drugs and exercise are the best-documented cofactors, although estrogens, angiotensin-converting enzyme inhibitors, β-blockers, lipid-lowering drugs, and alcohol have also been involved.

The mechanisms underlying anaphylaxis are complex and involve several interrelated pathways. Some of these pathways may be key to the development of anaphylaxis, while others may only modulate the severity of the reaction. An understanding of predisposing and augmenting factors could lead to the development of new prophylactic and therapeutic approaches.

Key words: Adenosine. Anaphylaxis. Cofactor. Exercise. IgE. IgG. Mast cell. NSAID.

Resumen

La anafilaxia se describe como una reacción aguda, con afectación multisistémica que puede causar la muerte del individuo que la padece, y que es consecuencia de una liberación súbita de mediadores originados en mastocitos y basófilos. Los alérgenos alimentarios son los desencadenantes más frecuentemente relacionados con las reacciones anafilácticas, suponiendo entre un 33 y un 56% de todos los casos y hasta un 81% de las anafilaxias en niños. Se considera que las anafilaxias en humanos están mediadas a través de la IgE, y los mastocitos y basófilos juegan un papel principal. Sin embargo, se han descrito otros mecanismos alternativos. De este modo, otros tipos celulares se han implicado en las reacciones anafilácticas, como es el caso de los neutrófilos o los macrófagos. La activación del complemento o del sistema de contacto, así como mecanismos mediados a través de la IgG, también han sido descritos. No todas las reacciones alérgicas acaban siendo una anafilaxia, de modo que se ha postulado la existencia de factores acompañantes (cofactores o factores potenciadores) que explicarían porque en algunos casos los alérgenos no son capaces de inducir una reacción alérgica o inducen una reacción leve, mientras que en otros casos desencadenan reacciones graves. Los cofactores se consideran relevantes hasta en el 30% de los episodios anafilácticos. En presencia de esos cofactores, las reacciones alérgicas pueden desarrollarse con concentraciones inferiores de alérgeno o ser más grave que en ausencia de ellos. Los antinflamatorios no esteroideos (AINE) y el ejercicio físico son los cofactores mejor conocidos, aunque se han descrito muchos otros, como los estrógenos, los inhibidores del enzima convertidor de la angiotensina, los β-bloqueantes, los hipolipemiantes o el alcohol.

Los mecanismos subyacentes en la anafilaxia son muy complejos y múltiples mecanismos parecen estar interrelacionados. Algunos de ellos pueden ser claves en el desarrollo de la anafilaxia, mientras que otros estarían únicamente modulando la gravedad de la reacción. La compresión de estos mecanismos es clave y permitirá el desarrollo de nuevas estrategias profilácticas y terapéuticas en la anafilaxia.

Palabras clave: Adenosina. AINE. Anafilaxia. Cofactor. Ejercicio. IgE. IgG. Mastocito.

Introduction

Anaphylaxis is an acute, life-threatening, multisystem syndrome resulting from the sudden release of mediators derived from mast cells and basophils [1]. Food allergens are the main triggers for anaphylaxis, accounting for 33%-56% of all cases and up to 81% of cases of anaphylaxis in children [2-4]. Therefore, this review focuses mainly on food-induced anaphylaxis.

Human anaphylaxis is generally thought to be mediated by IgE, with mast cells and basophils as key players, although alternative mechanisms have been proposed [5-7]. Several studies have revealed the complexity of mast cell signaling and the sensitivity of this system to regulation by individual pathways [8]. A wide variety of molecules contribute to the regulation of the allergic response, yet only a few can be classified as essential. Several reports have highlighted pathways/molecules that affect mast cell regulation and its threshold of activation. These molecules might play a key role in the release of mediators and in the pathophysiology of anaphylaxis [9]. The alternative pathways described in anaphylaxis arise from complement activation, neuropeptide release, T-cell activation, immune complex formation, cytotoxicity, IgG-dependent reactions, and involvement of purinergic metabolism [6,10]. However, most of these mechanisms are not fully understood.

The Classical Pathway: IgE, Mast Cells, and Basophils

The mechanism classically associated with human anaphylaxis is initiated by an allergen interacting with allergen-specific IgE bound to the FcεRI receptor on mast cells, basophils, or both. These allergens interact with IgE molecules on 2 or more receptors of the cell surface to cause cross-linking, which leads to receptor aggregation and initiates intracellular signaling. If signaling is sufficiently robust, mast cell/basophil activation and degranulation develop, with the release of preformed mediators, enzymes, and cytokines, such as histamine, tryptase, and tumor necrosis factor [8]. These mediators act directly on tissue to cause allergic symptoms and recruit/activate other inflammatory cells. The recruited cells release more mediators and stimulate the production of lipid-derived mediators such as prostaglandin D2 and cysteinyl leukotrienes, leading to amplification of the allergic reaction [11-13].

The process described above is likely an over-simplification of what actually occurs during an in vivo reaction, and several factors may influence antigen-dependent mast cell activation under specific conditions [14].

IgG-Mediated Reactions

IgG can bind to 6 different Fcgamma receptors (FcγR), namely, FcγRI, FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA, and FcγRIIIB, which are expressed with different affinities, downstream signaling, and pattern expression [15]. All 6 induce activation, except FcγRIIB, which mediates an inhibitory signal. FcγRI is considered to be the high-affinity receptor, although FcγRIIIB can bind IgG with high and low affinity depending on the IgG subclass.

The role of IgG in anaphylactic reactions has been demonstrated in mouse models. In a passive systemic anaphylaxis model, the allergen interacts with the specific IgG bound to FcγRIII on macrophages and basophils [5,7,16]. In this case, macrophage activation results mainly in the release of platelet-activating factor (PAF), rather than histamine [5,7]. The IgG-mediated pathway requires more antibody and antigen than the IgE-mediated pathway. In fact, IgG blocks IgE-dependent anaphylaxis when the individual is exposed to low doses of allergen. IgG either intercepts the antigen before it can cross-link mast cells/basophil–associated IgE or activates FcγRIIB, an inhibitory receptor. Furthermore, low doses of IgG are insufficient to induce IgG-mediated anaphylaxis, presumably because FcγRs have a much lower affinity than FcεRI (high-affinity IgE receptor) [5,7].

A previous study showed that the activation of FcγRIV receptors by IgG2 antibodies in neutrophils played a major role in mouse models of anaphylaxis [17]. Of note, neutrophils were not only sufficient, but played a dominant role in active systemic anaphylaxis. Neutrophils have been reported to be major PAF producers, and PAF secretion has been observed in mice undergoing neutrophil-dependent anaphylaxis [17,18]. Furthermore, PAF, rather than histamine, was the most important mediator in this type of anaphylaxis. However, release of PAF is not exclusively observed in IgG-mediated anaphylaxis, and some animal models have also demonstrated its presence in IgE-mediated reactions [8].

Although the existence of IgG-mediated anaphylaxis in humans remains unclear, some studies have shown that PAF, a mediator that seems to be associated with the IgG mechanism, is an essential mediator in human anaphylaxis. Vadas et al [19] showed that circulating PAF levels are increased and PAF acetylhydrolase (PAF-AH) activity is decreased in proportion to the severity of anaphylaxis. The biological half-life of PAF, which ranges from 3 to 13 minutes, is determined primarily by the rate of inactivation by PAF-AH [20]. Therefore, the slower the inactivation of PAF, the more severe the anaphylactic reaction may be. Patients with the lowest levels of PAF-AH activity are 27 times more at risk of severe or fatal anaphylaxis than patients with normal levels of PAF-AH activity. These and other studies suggest that PAF-AH deficiency predisposes to severe anaphylaxis [19,21].

The results of a recent study by Muñoz-Cano et al [10] suggest that both IgG and neutrophils may be involved in human anaphylaxis. In a group of patients with food anaphylaxis induced by lipid transfer proteins (LTP), the authors observed increased presence of specific anti-LTP IgG1 and IgG3 and increased expression of the 3 genes coding for the activating receptor FcγRI (CD64) [10]. Previous studies have demonstrated FcγRI-mediated human mast cell activation via IgG [22,23]. Both IgG1 and IgG3 bind to FcγRI, which is expressed in monocytes and macrophages and is inducible in neutrophils and mast cells [15,24]. FcγRI is the only Fc gamma receptor that binds to monomeric IgG (particularly IgG1 and IgG3) with high affinity. Muñoz-Cano et al found that LTP-allergic patients presented both specific IgG and anti-LTP IgE, suggesting that the activation of both IgG and IgE pathways may contribute substantially to the anaphylactic response. In

a study with patients allergic to galactose-alpha-1,3-alpha-galactose (α-gal), an allergen involved in allergy to red meat and cetuximab [25,26], Rispens et al [27] demonstrated the existence of both specific IgE and IgG anti–α-gal; these antibodies were IgG1.

As for the role of neutrophils in LTP-dependent anaphylaxis, Muñoz-Cano et al [10] showed, interestingly, that expression of markers of neutrophil activation and trafficking were significantly increased. Moreover, enhanced neutrophilic activity was suggested by elevated levels of reactive oxygen species/reactive nitrogen species, which are a measure of oxidative outburst. Many assumptions could be made based on the finding of specific IgG anti-LTP in patients with LTP-dependent anaphylaxis and existing evidence, although further studies are required to confirm them. These findings may suggest that the paradigm of IgE-mediated mast cell/basophil-induced food anaphylaxis is not totally accurate. In this particular case, LTP may be eliciting the allergic response via IgE, IgG, or both, activating not only mast cells and basophils, but also neutrophils. In any case, it is important to remember that other allergens may act similarly. Therefore, the possible combinations of cell types and Ig pathways involved in anaphylaxis are of significance.

Complement Activation in Anaphylaxis

Human mast cell activation via FcγRI-IgG constitutes a novel paradigm (see above). Although FcγRI receptors are normally occupied by serum monomeric IgG, this does not prevent their activation by IgG immune complexes. The latter have higher binding affinity and can therefore displace monomeric IgG and trigger hypersensitivity responses [24,28]. On the other hand, immune complexes also activate the complement system, generating anaphylatoxins such as C3a. C3a has a direct effect on mast cell activation in rat and in the human mast cell line HMC-1 [29]. Woolhiser et al [23] confirmed that C3a induced degranulation in $CD34^{+}$-derived human mast cells, although dramatic differences were observed between donors. Interestingly, C3a also demonstrated a synergistic effect with FcγRI activation, inducing a 2-fold increase in the release of FcγRI-induced

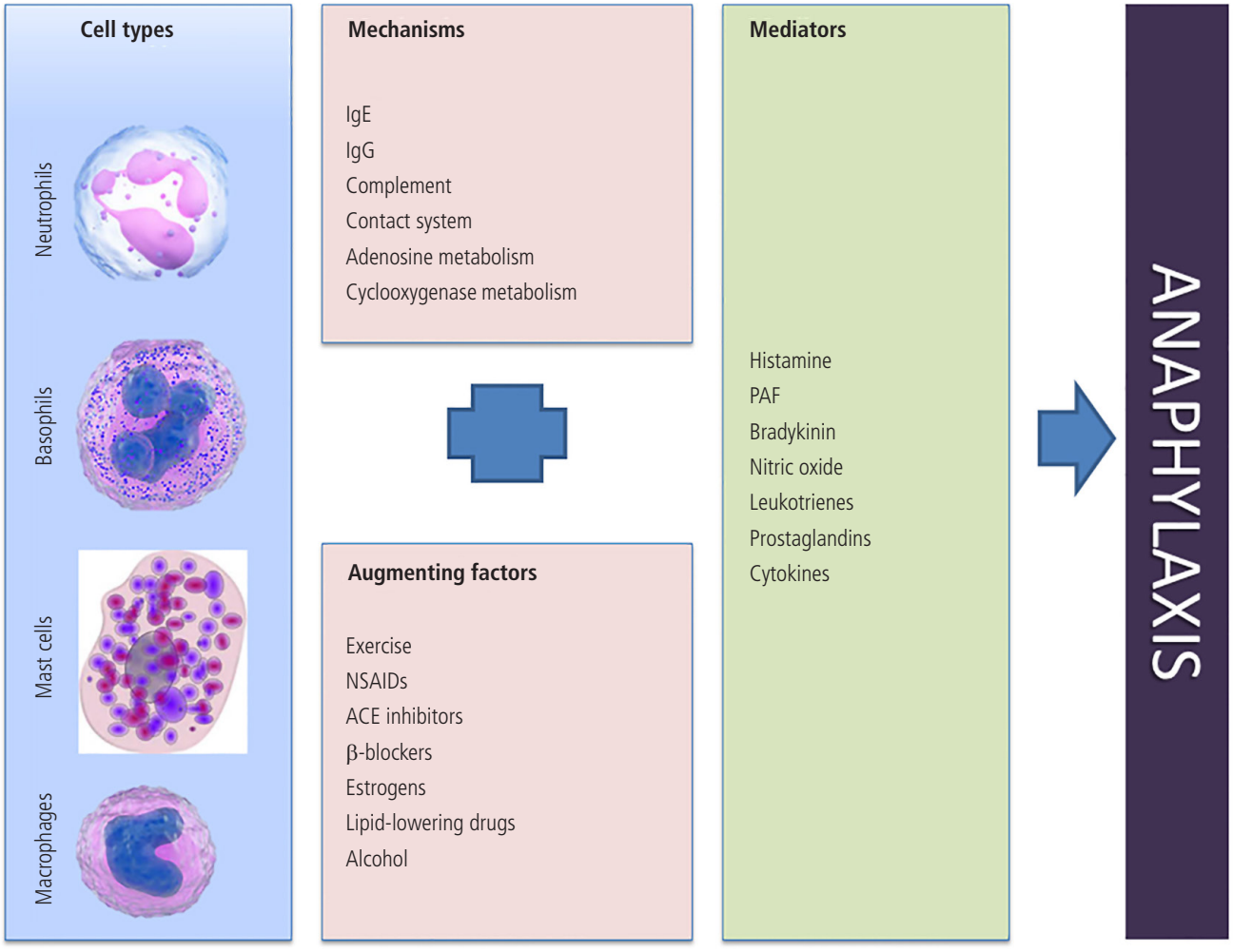

Figure. Mechanism of anaphylaxis. Ig indicates immunoglobulin; NSAID, nonsteroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme; PAF, platelet-activating factor..

β-hexosaminidase [23]. The combined effect of IgG and C3a results in greater mast cell activation or activation under circumstances in which neither of the stimuli would elicit maximal release on its own.

In a mouse model, Khodoun et al [30] demonstrated that peanut induces severe allergic reactions by Ig-independent activation of the complement system with production of large amounts of the anaphylatoxin C3a. Peanut activation of complement may synergize with the IgE response induced by the same allergen, contributing to the development of the characteristic severe reactions of these patients. The activation of complement by peanut in human plasma was also demonstrated in this study. Although the activation had a dose-dependent effect, its magnitude seemed lower than in the mouse model. In contrast, other allergens such as milk and egg white showed little ability to activate complement in human plasma [30]. Therefore, these results support that the severity of an allergic reaction depends not only on patient susceptibility [10] or presence of cofactor [31], but also on intrinsic characteristics of the allergen.

Activation of complement in the absence of immune complex formation has been proposed to account for reactions with drugs solubilized in therapeutic liposomes and lipid-based excipients. Cremophor EL was the diluent of the older preparations of propofol and paclitaxel; it formed large micelles with serum lipids and cholesterol that could stimulate complement activation under physiological conditions [32]. Complement activation leads to the release of C3a, C5a, and C5b-9, which trigger activation of mast cells, basophils, and other cells via their specific receptors. Although from a clinical point of view these reactions cannot be differentiated from IgE-mediated reactions, they do have specific characteristics. These reactions mostly arise upon first treatment, in patients who have not previously been exposed to the drugs, and re-exposures are related to milder or no reactions. Moreover, the reactions respond to the infusion rate and premedication with corticosteroids and antihistamines. Interestingly, there is substantial interindividual variation, and sensitivity to a specific liposome does not necessarily imply sensitivity to others [33].

Contact System Activation in Anaphylaxis

Direct or indirect activation of the intrinsic blood coagulation pathway in IgE-mediated reactions has been described [34]. A recent study demonstrated how heparin levels increase and the factor XII-driven contact system becomes activated during anaphylaxis, resulting in production of bradykinin [35]. The effect of heparin as a trigger of contact activation–mediated bradykinin formation was suggested around the end of 2007, after analysis of a series of heparin-induced anaphylactic shocks in the United States and Germany. More than 150 patients died from anaphylactic shock associated with oversulfated chondroitin sulfate–contaminated heparin [36]. The contaminated heparins were shown to activate factor XII and trigger bradykinin formation [37]. Bradykinin was therefore thought to play a key role in anaphylactic shock, and targeting its generation seems to be a promising strategy for treatment of anaphylaxis. Bradykinin induces hypotension via the bradykinin type 2 receptor, and blockage using a commercially available antagonist such as icatibant could be a valid therapeutic option [38].

Role of Cofactors or Augmenting Factors in Anaphylaxis

Not all allergic reactions are anaphylactic, and the presence of the so-called accompanying factors could explain why some conditions lead to anaphylaxis, while in other cases, the allergen elicits a milder reaction or is even tolerated. In the presence of cofactors, allergic reactions may be induced at lower doses of allergen or become more severe and are reported to be relevant in up to 30% of episodes of anaphylaxis [31,39]. Recently, Niggermann and Beyer [40] proposed 3 categories of risks factors for anaphylaxis: first, the *augmenting factors*, such as physical exercise, acute infections, drugs (nonsteroidal anti-inflammatory drugs [NSAIDs], proton pump inhibitors [PPI]), alcohol, and menstruation, which influence the immunological mechanism of type I allergy; second, *concomitant diseases*, which are related to more severe reactions and/or increased mortality and include asthma, mastocytosis, and cardiovascular diseases; and third, *cofactors*, which are defined as a subgroup of risk factors with no influence on the allergen–IgE reaction. Examples of this category are psychological factors (eg, emotional stress), angiotensin-converting enzyme (ACE) inhibitors, or specific allergens. However, and considering the general lack of knowledge about the mechanisms underlying these risk factors, they can hardly be so strictly classified. Therefore, for the purposes of this review, the terms cofactor and augmenting factor are used indistinctively.

Estrogens

Several clinical studies have suggested sex differences in the incidence of anaphylaxis, showing that adult women experience anaphylaxis more often than men [41,42]. However, these differences are only observed during the reproductive years, but not the prepubertal years, suggesting that sex hormones might be involved [42]. Furthermore, recurrent episodes of anaphylaxis around the time of menstruation have been reported, suggesting that estrogens or progesterone might be involved in susceptibility to anaphylaxis [43]. Similarly, exacerbations associated with the menstrual cycle are well documented in patients with urticaria and asthma [44,45].

The increased susceptibility to anaphylaxis in females noted in clinical studies was recently reproduced in a mouse model of systemic anaphylaxis constructed by Hox et al [46]. The ablation of the major source of sex hormones in female mice by ovariectomy resulted in a reduction in the severity of anaphylaxis compared with nonovariectomized animals. Moreover, subcutaneous implantation of estradiol-releasing pellets into ovariectomized mice restored the severity of the anaphylactic reaction, suggesting that these sex differences were estradiol-dependent. However, ovariectomized animals showed similar serum concentrations of mast cell mediators such as histamine or IL-6, indicating that the estrogen effect was not due to enhancement of the IgE-mediated mast cell response. Interestingly, the authors found evidence of

increased vascular permeability in female mice experiencing anaphylaxis than in male mice, suggesting that estrogens may promote vascular leakage. In fact, female mice showed higher expression of endothelial nitric oxide synthase (eNOS), the enzyme responsible for the production of nitric oxide (NO). Collectively, the data provide evidence that estradiol upregulates eNOS expression and subsequent NO production, which proved to be critical for increased vascular permeability and severe anaphylaxis in female mice [46].

Exercise

Although physical exercise is one of the best-known augmenting factors, its precise pathogenic mechanism remains poorly understood. Nevertheless, some theories have been proposed. Several causative foods have been identified in food-dependent exercise-induced anaphylaxis (FDEIA), including shellfish, vegetables, fruits, nuts, and eggs; however, wheat (particularly ω-5 gliadin) is the most frequent one [47]. Thus, most mechanistic studies have been performed in patients with wheat-dependent exercise-induced anaphylaxis (WDEIA).

One of the hypotheses in WDEIA suggests that activation of tissue transglutaminase (tTG) during exercise could create large ω-5 gliadin/tTG complexes capable of eliciting anaphylactic reactions in patients with WDEIA. Palosuo et al [48] show that the IgE-binding ability of ω-5 gliadin remains unaltered after pepsin/trypsin digestion, and digested peptides form high-molecular-weight complexes together with tTG. Moreover, allergen-tTG complexes make IgE-mediated reactions considerably more likely both in vivo and in vitro than allergen alone. However, no direct evidence has been found of tTG activation in response to exercise or the presence of ω-5 gliadin/tTG complexes in patients with WDEIA [48].

An increase in the intestinal allergen absorption induced by exercise [49] has been proposed as a mechanism for WDEIA [50]. Studies in animal models of food allergy have shown that physical exercise affects the absorption of antigen from the gastrointestinal tract owing to gastrointestinal mucosal damage [51,52]. Proteins are mostly transported across the intestinal epithelium via the paracellular pathway through the space between the epithelial cells, which is regulated by tight junctions. Prolonged or intense exercise increases core temperature, leading to epithelial cell damage. In addition, exercise redirects blood flow away from the splanchnic arteries to the working muscle, leading to an ischemia/reperfusion cycle that can result in oxidative damage. Both thermal and ischemic stress can affect the phosphorylation state of tight junction proteins, resulting in increased permeability and allergen absorption [53,54]. Matsuo et al [55] demonstrated that gliadin serum levels increase in accordance with allergy symptoms when wheat and exercise are combined in patients with WDEIA, suggesting that gliadin serum levels are a key factor in the induction of symptoms and that the increase in intestinal permeability accounts for the elevated gliadin levels found in patients with WDEIA.

A third hypothesis suggests that exercise, owing to a direct effect on mast cells, would lower the threshold for IgE-mediated mast cell degranulation in patients with WDEIA. It is known that physical exercise results in increased plasma osmolarity [56] and changes in osmolarity activate mast cells to release inflammatory mediators [57]. Along the same lines, Khamnei et al [56] showed an increase in skin response to compound 48/80 (a marker of skin mast cell releasability) after the ingestion of food allergen combined with exercise. However, food allergen or exercise alone did not enhance 48/80-induced skin reaction. A previous study demonstrated in vitro that the combination of 2 triggers, IgE activation and hyperosmolar stimuli, had a synergistic effect on IgE-induced mast cell release [58].

Lipid-Lowering Drugs

The circulating active form of PAF-AH, also known as lipoprotein-associated phospholipase A2, circulates mostly as a complex with low-density lipoproteins (LDL) [20]. Plasma PAF-AH concentration correlates directly with LDL levels, and a decrease in LDL results in a reduction in PAF-AH levels. Since the catalytic activity of PAF-AH is also regulated by its association with LDL, lowering LDL in plasma results in an increase in the half-life of PAF [59]. Thus, drugs that lower LDL levels (statins) reduce PAF-AH plasma levels and activity and prolong the half-life of PAF. Most studies have been performed in normolipidemic individuals rather than in patients with hypercholesterolemia and show increased PAF-AH levels and activity in the latter. Perelman et al [60] evaluated the correlation between PAF-AH and LDL levels in individuals with peanut allergy and found a significant direct correlation between LDL levels and PAF-AH activity. The results reported suggest that pharmacologically lowering LDL levels in patients at risk for anaphylaxis may lower PAF-AH activity [19] and inadvertently increase the risk of severe or fatal anaphylaxis. However, further epidemiological studies are needed to confirm lipid-lowering drugs as a risk factor in anaphylaxis.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs have been reported to be present in up to 22% of cases of food-induced anaphylactic shock, representing a risk factor with an odds ratio >11 [61]. In the Mediterranean area, NSAIDs account for up to 58% of cases of cofactor-induced food-related anaphylaxis [62] and are present in up to 33% of cases of anaphylaxis induced by LTP [63]. The result of in vitro tests showed that NSAIDs exacerbate food allergy in patients diagnosed with FDEIA [64], despite NSAIDs not being originally involved in the reactions. Although the synergistic effect of NSAIDs and food allergy is well known, very few clinical studies have demonstrated it, and even fewer studies have investigated the underlying mechanism. Two main hypotheses have been proposed to explain food-dependent NSAID-induced anaphylaxis (FDNIA). The first suggests that NSAIDs increase the permeability of the intestinal barrier, thus causing major allergen absorption [50]. Another hypothesis suggests that the direct effect of NSAIDs on mast cells and basophils amplifies degranulation/activation [65,66], although the mechanisms involved remain to be elucidated.

Inhibition of cyclooxygenase (COX), which in turn inhibits the production of prostaglandins, is the main anti-inflammatory action of NSAIDs. Unfortunately, prostaglandins play a major role in many physiological processes, such as gastrointestinal mucosal defense and repair [67]. NSAIDs leave gastrointestinal tissues more susceptible to the damage induced by gastric acid

and bile and less able to restore mucosal function. Furthermore, NSAIDs have the ability to induce mitochondrial injury and thus to damage intestinal epithelial cells and increase intestinal permeability [68,69]. Although samples are small in the few available studies, both aspirin and exercise have been shown to increase serum gliadin levels in patients with WDEIA [50,65]. The authors suggest that the facilitation of gliadin absorption from the gastrointestinal tract damaged by aspirin could cause the increased serum gliadin levels observed in WDEIA. A similar increase in serum gliadin levels was also observed in healthy individuals, although the dose of aspirin in the controls was double that taken by WDEIA patients. Specific sensitization affects the increase in gastrointestinal allergen uptake across the intestinal epithelium in several models of allergy and would account for the differences observed between groups [52].

Bartra et al [70] suggested that the enhancing effect of NSAIDs could be mediated by the COX pathway. This theory would be supported by the enhanced activation observed when basophils from patients with FDNIA are incubated with allergen and aspirin compared with activation using allergen alone. Several authors [71-73] showed that the enhancement of the IgE response was an NSAID class effect and thus related to their capability to inhibit COX enzymes. Furthermore, previous studies have demonstrated a correlation between both the dose of aspirin and the degree of COX inhibition [55,71,74] and the enhancement of the allergic reaction [71]. Conversely, as occurs in aspirin-induced asthma, nimesulide [75] and etodolac [65,76] (selective COX-2 inhibitors) did not increase allergic reactions. Finally, prostaglandin E1, a known product of the COX pathway [77], has shown a protective effect in FDNIA [78]. Prostaglandin E2 (PGE_2), another product of COX metabolism, has been reported to enhance antigen-dependent degranulation in cultures of peripheral blood–derived human mast cells through 2 of its receptors, EP1 and EP3 [79]. In contrast, PGE_2 inhibits IgE-mediated production of histamine, PGD2, LTC4, and TNF-α via the EP2 receptor [80]. Thus, the relative balance between the expressions of these receptors may determine the activation or inhibition of mast cells via EP receptors. However, little is known about relative expression of EP on the mast cells of individuals with food anaphylaxis.

Adenosine metabolism has been involved in several diseases exacerbated by NSAIDs. Adenosine can produce contrasting responses in mast cell activation; it is reported to potentiate production of IL-4 and IL-8 in the human mast cell line HMC-1 and to enhance FcεRI-mediated degranulation in both mouse and human lung mast cells. In contrast, adenosine has also been reported to inhibit IgE-mediated degranulation of human mast cells [81,82]. Such diverse responses are attributable to the multiple receptors (purinergic receptors) expressed on mast cells (A2AR, A2BR, A3R), as occurs with PGE_2 receptors (EP). A high transcript variant of the A3R gene (*ADORA3*) has been described in NSAID-dependent urticaria [83], and genetic polymorphisms of adenosine receptors A1 (ADORA1) and A2A (ADORA2A) were associated with aspirin-induced asthma [84]. Although these diseases are independent of IgE and the clinical manifestations are different, they all involve NSAIDs and alteration of adenosine metabolism. A recent study evaluating the transcriptome of patients with NSAID-dependent food anaphylaxis revealed overexpression of genes involved in adenosine metabolism, particularly *ADORA3* [10].

A3R activation has antagonistic effects depending on the cell type. Several mouse models have demonstrated its anti-inflammatory effect, which results from the inhibition of cytokines such as IFN-γ [85]. However, A3R activation also potentiates FcεRI-induced degranulation in human mast cells and thus contributes to allergic inflammation [86-88]. A link between NSAIDs, adenosine receptors, and allergic inflammation was suggested by the finding that NSAIDs inhibit oxidative phosphorylation and promote hydrolysis of ATP with the release of adenosine [89,90]. Furthermore, a link between adenosine and COX metabolism has also been established. Adenosine has been reported to inhibit mast cell degranulation via the A2A receptor [91], and although the exact inhibitory mechanism is not known, A2A activation was shown to increase COX-2 expression and thus PGE_2 production. On the other hand, COX-2 inhibition potentiates A3R activation [92]. Oversimplifying, in patients with FDNIA, adenosine released by the effect of NSAIDs would activate 2 receptors with opposing effects, namely, A2AR and A3R. Whereas A2AR activation would increase PGE_2 production and inhibit mast cell activation, A3R would potentiate the IgE-mediated response. However, owing to the inhibitory effect of COX-2 mediated by NSAIDs, the protective production of PGE_2 would also be reduced, thus favoring mast cell activation via A3R (overexpressed [10]).

Clearly, the mechanisms underlying FDNIA are quite complex, and several pathways are intertwined. Thus, further studies are needed to explore the various alternatives beyond and complementary to the IgE mechanism.

Angiotensin-Converting Enzyme Inhibitors and β-Blockers

ACE inhibitors and β-blockers have been reported to be augmenting factors in anaphylaxis [93-95]. Moneret-Vautrin and Latarche [94] reported an odds ratio of 6.8 for β-blockers and 13 for ACE inhibitors. Conversely, other studies found that these drugs were not associated with an increased risk of reaction [21,96]. Indeed, a recent epidemiological study in a German-speaking population did not find a significant increase in odds ratios for patients who used ACE inhibitors and β-blockers separately [97]. However, their combined use increased risk in patients with severe anaphylaxis (grade III/IV). Interestingly, mast cells were recently identified as direct targets of ACE inhibitors and β-blockers [97], thus supporting the augmenting effect of these drugs in anaphylaxis. In their mouse model, the authors found that single treatment slightly enhanced mast cell degranulation triggered by the IgE receptor and that no effect was observed when the drugs were used without IgE activation. Moreover, in the aforementioned epidemiological study [97], the combination of ACE inhibitors and β-blockers significantly augmented mast cell releasability through FcεRI. Despite this new evidence, caution is advised when extrapolating the results to human anaphylaxis. Further epidemiological and in vitro studies in humans are needed to confirm whether β-blockers and ACE inhibitors worsen anaphylaxis.

Alcohol

Alcohol is always listed as a cofactor in anaphylaxis, although data on its involvement in anaphylaxis or in the

underlying pathogenic mechanisms are limited. Alcohol consumption is present in up to 15.2% of cases of anaphylaxis in some series [98], regardless of severity [97]. The pathogenic mechanism is not well known, but an increase in intestinal allergen absorption has been postulated. Alcohol induces a change in the expression of the tight junction–associated proteins ZO-1 and claudin-1, thus increasing the permeability of the intestinal epithelial barrier [99].

Alcohol increases extracellular adenosine by inhibiting adenosine uptake [100]. Interestingly, after prolonged exposure to ethanol, cells become tolerant to the acute effects of ethanol on adenosine transport, and adenosine uptake is no longer inhibited [100]. As suggested in NSAIDs, an adenosine-related mechanism could be involved in alcohol-enhanced anaphylaxis. Indeed, an acute increase in extracellular adenosine levels would account for the potentiation induced by acute intake of alcohol, which is not observed in chronic alcohol consumption. Indeed, an adenosine-mediated effect could also partly justify (together with the increase in intestinal permeability) the potentiation effect of alcohol observed in patients with FDEIA in the absence of exercise, even though alcohol was not implicated in the original reaction [50,65,101].

Another hypothetical mechanism in alcohol-enhanced anaphylaxis could be the ability of alcohol to increase the serum IgE concentration [102]. In a mouse model, acute alcohol intake was associated with an increase in serum IgE and a decrease in serum IgG levels [102]. Chronic consumption has also been related to other immunological abnormalities, namely, a shift toward T_H2 and an impairment of the immune response (IgG) to systemic vaccines [103]. Heavy drinkers frequently show serum specific IgE to cross-reactive carbohydrate determinants from wine, although this sensitization is asymptomatic. Furthermore, serum tryptase level, which is negatively associated with acute consumption, is lower in heavy drinkers than in healthy individuals. In conclusion, alcohol intake has contradictory effects: while it seems to predispose to allergic reactions, it is also associated with lower mast cell–related mediator production.

Conclusion

The mechanisms underlying anaphylaxis are complex and involve several interrelated pathways. Further studies exploring mechanisms beyond classic IgE activation are needed. Some pathways may play a key role in the development of anaphylaxis, while others may only modulate the severity of the reaction. An understanding of the predisposing and augmenting factors could facilitate the development of new prophylactic and therapeutic approaches. Ideally, these strategies should be patient-oriented, based on the characteristics of the eliciting allergen and the particularities of the reactions, and should target the specific pathways involved.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS,Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP,Decker WW l. Second symposium on the definition and management of anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006;117:391-7.
2. Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. Allergy. 2011;66:1-14.
3. Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N, Vierucci A. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985-1996). Ann Allergy Asthma Immunol. 2001;87:27-32.
4. Wang J, Sampson HA. Food anaphylaxis. Clin Exp Allergy. 2007;37:651-60.
5. Finkelman FD. Anaphylaxis: Lessons from mouse models. J Allergy Clin Immunol. 2007;120:506-15.
6. Metcalfe DD, Peavy RD, Gilfillan AM. Mechanisms of mast cell signaling in anaphylaxis. J Allergy Clin Immunol. 2009;124:639-46.
7. Strait RT, Morris SC, Yang M, Qu XW, Finkelman FD. Pathways of anaphylaxis in the mouse. J Allergy Clin Immunol. 2002;109:658-68.
8. Rivera J, Gilfillan A. Molecular regulation of mast cell activation. J Allergy Clin Immunol. 2006;117:1214-25.
9. Metcalfe DD, Peavy RD, Gilfillan AM. Mechanisms of mast cell signaling in anaphylaxis. J Allergy Clin Immunol. 2009;124:639-46; quiz 647-8.
10. Muñoz-Cano R, Pascal M, Bartra J, Picado C, Valero A, Kim DK, Brooks S, Ombrello M, Metcalfe DD, Rivera J, Olivera A. Distinct transcriptome profiles differentiate nonsteroidal anti-inflammatory drug-dependent from nonsteroidal anti-inflammatory drug-independent food-induced anaphylaxis. J Allergy Clin Immunol. 2016;137(1):137-46.
11. Kemp SF, Lockey RF. Anaphylaxis: A review of causes and mechanisms. J Allergy Clin Immunol. 2002;110:341-8.
12. Kajiwara N, Sasaki T, Bradding P, Cruse G, Sagara H, Ohmori K, Saito H, Ra C, Okayama Y. Activation of human mast cells through the platelet-activating factor receptor. J Allergy Clin Immunol. 2010;125:1137-45.
13. Theoharides TC, Alysandratos KD, Angelidou A, Delivanis DA, Sismanopoulos N, Zhang B, Asadi S, Vasiadi M, Weng Z, Miniati A, Kalogeromitros D. Mast cells and inflammation. Biochim Biophys Acta. 2012;1822:21-33.
14. Gilfillan AM, Tkaczyk C. Integrated signalling pathways for mast-cell activation. Nat Rev Immunol. 2006;6:218-30.
15. Bruhns P. Properties of mouse and human IgG receptors and their contribution to disease models. Blood. 2012;119:5640-9.
16. Tsujimura Y, Obata K, Mukai K, Shindou H, Yoshida M, Nishikado H, Kawano Y, Minegishi Y, Shimizu T, Karasuyama H. Basophils Play a Pivotal Role in Immunoglobulin-G-Mediated but Not Immunoglobulin-E-Mediated Systemic Anaphylaxis. Immunity. 2008;28:581-9.

17. Jönsson F, Mancardi DA, Kita Y, Karasuyama H, Iannascoli B, Van Rooijen N, Shimizu T, Daëron M, Bruhns P. Mouse and human neutrophils induce anaphylaxis. J Clin Invest. 2011;121:1484-96.
18. DeNichilo MO, Stewart AG, Vadas MA, Lopez AF. Granulocyte-macrophage colony-stimulating factor is a stimulant of platelet-activating factor and superoxide anion generation by human neutrophils. J Biol Chem. 1991;266:4896-902.
19. Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T, Simons FE ,Simons KJ, Cass D, Yeung J. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N Engl J Med. 2008;358:28-35.
20. Stafforini DM. Biology of platelet-activating factor acetylhydrolase (PAF-AH, lipoprotein associated phospholipase A2). Cardiovasc Drugs Ther. 2009;23:73-83.
21. Brown SGA, Stone SF, Fatovich DM, Burrows SA, Holdgate A, Celenza A, Coulson A, Hartnett L, Nagree Y, Cotterell C, Isbister GK. Anaphylaxis: clinical patterns, mediator release, and severity. J Allergy Clin Immunol. 2013;132:1141-9.
22. Okayama Y, Hagaman DD, Metcalfe DD. A comparison of mediators released or generated by IFN-γ-treated human mast cells following aggregation of FcγRI or FcεRI1. J Immunol. 2001;166:4705-12.
23. Woolhiser MR, Brockow K, Metcalfe DD. Activation of human mast cells by aggregated IgG through FcgammaRI: additive effects of C3a. Clin Immunol. 2004;110:172-80.
24. Mancardi DA., Albanesi M, Jönsson F, Iannascoli B, Van Rooijen N, Kang X, England P, Daëron M, Bruhns P. The high-affinity human IgG receptor FcγRI (CD64) promotes IgG-mediated inflammation, anaphylaxis, and antitumor immunotherapy. Blood. 2013;121:1563-73.
25. Apostolovic D, Tran TAT, Sánchez-Vidaurre S, Cirkovic Velickovic T, Starkhammar M, Hamsten C, van Hage M. Red meat allergic patients have a selective IgE response to the α-Gal glycan. Allergy. 2015;70:1497-500.
26. Chung CH, Mirakhur B, Chan E, Le Q-T, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TA. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med. 2008;358:1109-17.
27. Rispens T, Derksen NIL, Commins SP, Platts-Mills TA, Aalberse RC. IgE production to α-gal is accompanied by elevated levels of specific IgG1 antibodies and low amounts of IgE to blood group B. PLoS One. 2013;8:e55566.
28. van der Poel CE, Spaapen RM, van de Winkel JGJ, Leusen JHW. Functional Characteristics of the High Affinity IgG Receptor, Fc{gamma}RI. J Immunol. 2011;186:2699-704.
29. Zwirner J, Götze O, Sieber A, Kapp A, Begemann G, Zuberbier T, Werfel T. The human mast cell line HMC-1 binds and responds to C3a but not C3a(desArg). Scand J Immunol. 1998;47:19-24.
30. Khodoun M, Strait R, Orekov T, Hogan S, Karasuyama H, Herbert DR, Köhl J, Finkelman FD. Peanuts can contribute to anaphylactic shock by activating complement. J Allergy Clin Immunol. 2009;123:342-51.
31. Wölbing F, Fischer J, Köberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. Allergy Eur J Allergy Clin Immunol. 2013;68:1085-92.
32. Szebeni J, Muggia FM, Alving CR. Complement activation by Cremophor EL as a possible contributor to hypersensitivity to paclitaxel: an in vitro study. J Natl Cancer Inst. 1998;90:300-6.
33. Szebeni J, Muggia F, Gabizon A, Barenholz Y. Activation of complement by herapeutic liposomes and other lipticts: Prediction and preventiond excipient-based therapeutic products. Adv Drug Deliv Rev. 2011;63:1020-30.
34. Pinckard RN, Tanigawa C, Halonen M. IgE-induced blood coagulation alterations in the rabbit: consumption of coagulation factors XII, XI, and IX in vivo. J Immunol. 1975;115:525-32.
35. Sala-Cunill A, Björkqvist J, Senter R, Guilarte M, Cardona V, Labrador M, Nickel KF, Butler L, Luengo O, Kumar P, Labberton L, Long A, Di Gennaro A, Kenne E, Jämsä A, Krieger T, Schlüter H, Fuchs T, Flohr S, Hassiepen U, Cumin F, McCrae K, Maas C, Stavrou E, Renné T. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. J Allergy Clin Immunol. 2015;135:1031-43.
36. Guerrini M, Beccati D, Shriver Z, Naggi A, Viswanathan K, Bisio A, Capila I, Lansing JC, Guglieri S, Fraser B, Al-Hakim A, Gunay NS, Zhang Z, Robinson L, Buhse L, Nasr M, Woodcock J, Langer R, Venkataraman G, Linhardt RJ, Casu B, Torri G, Sasisekharan R. Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events. Nat Biotechnol. 2008;26:669-75.
37. Kishimoto TK, Viswanathan K, Ganguly T, Elankumaran S, Smith S, Pelzer K, Lansing JC, Sriranganathan N, Zhao G, Galcheva-Gargova Z, Al-Hakim A, Bailey GS, Fraser B, Roy S, Rogers-Cotrone T, Buhse L, Whary M, Fox J, Nasr M, Dal Pan GJ, Shriver Z, Langer RS, Venkataraman G, Austen KF, Woodcock J, Sasisekharan R. Contaminated heparin associated with adverse clinical events and activation of the contact system. N Engl J Med. 2008;358:2457-67.
38. Siebeck M, Cheronis JC, Fink E, Kohl J, Spies B, Spannagl M, Jochum M, Fritz H. Dextran sulfate activates contact system and mediates arterial hypotension via B2 kinin receptors. J Appl Physiol. 1994;77:2675-80.
39. Worm M, Edenharter G, Ruëff F, Scherer K, Pföhler C, Mahler V, Treudler R, Lang R, Nemat K, Koehli A, Niggemann B, Hompes S. Symptom profile and risk factors of anaphylaxis in Central Europe. Allergy Eur J Allergy Clin Immunol. 2012;67:691-8.
40. Niggemann B, Beyer K. Factors augmenting allergic reactions. Allergy 2014;69:1582-7.
41. Webb LM LP. Anaphylaxis: a review of 601 cases. J Allergy Clin Immunol. 2006;97:39-43.
42. Liew WK, Williamson E, Tang MLK. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol. 2009;123:434-42.
43. Bauer CS, Kampitak T, Messieh ML, Kelly KJ, Vadas P. Heterogeneity in presentation and treatment of catamenial anaphylaxis. Ann Allergy Asthma Immunol. 2013;111:107-11.
44. Vasconcelos C, Xavier P, Vieira a P, Martinho M, Rodrigues J, Bodas A, Barros MA, Mesquita-Guimarães J. Autoimmune progesterone urticaria. Gynecol Endocrinol. 2000;14:245-7.
45. Pereira Vega A, Sanchez Ramos JL, Maldonado Perez JA, Alvarez Gutierrez FJ, Ignacio Garcia JM, Vazquez Oliva R, Romero Palacios P, Bravo Nieto JM, Sánchez Rodríguez I, Gil Muñoz F. Variability in the prevalence of premenstrual asthma. Eur Respir J. 2010;35:980-6.

46. Hox V, Desai A, Bandara G, Gilfillan AM, Metcalfe DD, Olivera A. Estrogen increases the severity of anaphylaxis in female mice through enhanced endothelial nitric oxide synthase expression and nitric oxide production. J Allergy Clin Immunol. 2015;135:729-36.e5.
47. Morita E, Kunie K, Matsuo H. Food-dependent exercise-induced anaphylaxis. J Dermatol Sci. 2007;47:109-17.
48. Palosuo K, Varjonen E, Nurkkala J, Kalkkinen N, Harvima R, Reunala T, Alenius H. Transglutaminase-mediated cross-linking of a peptic fraction of ω-5 gliadin enhances IgE reactivity in wheat-dependent, exercise-induced anaphylaxis. J Allergy Clin Immunol. 2003;111:1386-92.
49. Lambert GP, Broussard LJ, Mason BL, Mauermann WJ, Gisolfi CV. Gastrointestinal permeability during exercise: effects of aspirin and energy-containing beverages. J Appl Physiol. 2001;90:2075-80.
50. Matsuo H, Morimoto K, Akaki T, Kaneko S, Kusatake K, Kuroda T, Niihara H, Hide M, Morita E. Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. Clin Exp Allergy. 2005;35:461-6.
51. Yano H, Kato Y, Matsuda T. Acute exercise induces gastrointestinal leakage of allergen in lysozyme-sensitized mice. Eur J Appl Physiol. 2002;87:358-64.
52. Sakamoto Y, Ohtsuka T, Yoshida H, Ohto K, Onobori M, Matsumoto T, Iikura Y, Morohoshi T. Time course of changes in the intestinal permeability of food-sensitized rats after oral allergen challenge. Pediatr Allergy Immunol. 1998;9:20-4.
53. Zuhl M, Schneider S, Lanphere K, Conn C, Dokladny K, Moseley P. Exercise regulation of intestinal tight junction proteins. Br J Sports Med. 2014;48:980-6.
54. Phillips TE, Phillips TL, Neutra MR. Macromolecules can pass through occluding junctions of rat ileal epithelium during cholinergic stimulation. Cell Tissue Res. 1987;247:547-54.
55. Matsuo H, Yokooji T, Morita H, Ooi M, Urata K, Ishii K, Takahagi S, Yanase Y, Hiragun T, Mihara S, Hide M. Aspirin augments IgE-mediated histamine release from human peripheral basophils via Syk kinase activation. Allergol Int. 2013;62:503-11.
56. Khamnei S, Alipour MR, Ahmadiasl N. The Combined Effects of Exercise and Post Dehydration Water Drinking on Plasma Argenine Vasopressin, Plasma Osmolality and Body Temperature in Healthy Males. J Endocrinol Metab. 2005;2:80-6.
57. Torres-Atencio I, Ainsua-Enrich E, de Mora F, Picado C, Martín M. Prostaglandin E2 prevents hyperosmolar-induced human mast cell activation through prostanoid receptors EP2 and EP4. PLoS One. 2014;9:e110870.
58. Eggleston P a, Kagey-Sobotka a, Schleimer RP, Lichtenstein LM. Interaction between hyperosmolar and IgE-mediated histamine release from basophils and mast cells. Am Rev Respir Dis. 1984;130:86-91.
59. Caslake MJ, Packard CJ, Suckling KE, Holmes SD, Chamberlain P, Macphee CH. Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase: a potential new risk factor for coronary artery disease. Atherosclerosis. 2000;150:413-9.
60. Perelman B, Adil A, Vadas P. Relationship between platelet activating factor acetylhydrolase activity and apolipoprotein B levels in patients with peanut allergy. Allergy Asthma Clin Immunol. 2014;10:20.
61. Moneret-Vautrin D-A, Latarche C. Drugs as risk factors of food anaphylaxis in adults: AA case-control study. Bull Acad Natl Med. 2009;193:351-63.
62. Cardona V, Luengo O, Garriga T, Labrador-Horrillo M, Sala-Cunill A, Izquierdo A, Soto L, Guilarte M. Co-factor-enhanced food allergy. Allergy. 2012;67:1316-8.
63. Pascal M, Muñoz-Cano R, Reina Z, Palacín A, Vilella R, Picado C, Juan M, Sánchez-López J, Rueda M, Salcedo G, Valero A, Yagüe J, Bartra J. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. Clin Exp Allergy. 2012;42:1529-39.
64. Harada S, Horikawa T, Ashida M, Kamo T, Nishioka E, Ichihashi M. Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis. Br J Dermatol. 2001;145:336-9.
65. Aihara M, Miyazawa M, Osuna H, Tsubaki K, Ikebe T, Aihara Y, Ikezawa Z. Food-dependent exercise-induced anaphylaxis: Influence of concurrent aspirin administration on skin testing and provocation. Br J Dermatol. 2002;146:466-72.
66. Matsukura S, Aihara M, Sugawara M, Kunimi Y, Matsuki M, Inoue Y, Kambara T, Ikezawa Z. Two cases of wheat-dependent anaphylaxis induced by aspirin administration but not by exercise. Clin Exp Dermatol. 2010;35:233-7.
67. Wallace JL. Mechanisms, prevention and clinical implications of nonsteroidal anti-inflammatory drug-enteropathy. World J Gastroenterol. 2013;19:1861-76.
68. Bjarnason I, Takeuchi K. Intestinal permeability in the pathogenesis of NSAID-induced enteropathy. J Gastroenterol. 2009;44:23-9.
69. Wallace JL, de Nucci G, Sulaieva O. Toward More GI-Friendly Anti-Inflammatory Medications. Curr Treat Options Gastroenterol. 2015;13:377-85.
70. Bartra J, Pascal M, Vilella R, Mila J, Muñoz-Cano R, Sanchez-Lopez J, Valero A PC. In Vitro Evidence Of The Synergistic Effect Of Non Steroidal Anti Inflammatory Drugs (NSAIDs) Into Ig-E Mediated Food Allergy Response In Basophils. J Allergy Clin Immunol. 2011;127:AB185.
71. Wojnar RJ, Hearn T, Starkweather S. Augmentation of allergic histamine release from human leukocytes by nonsteroidal anti-inflammatory-analgesic agents. J Allergy Clin Immunol. 1980;66:37-45.
72. Knights KM, Mangoni AA, Miners JO. Defining the COX inhibitor selectivity of NSAIDs: implications for understanding toxicity. Expert Rev Clin Pharmacol. 2010;3:769-76.
73. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, Brockow K, Campo P, Celik G, Cernadas J, Cortellini G, Gomes E, Niżankowska-Mogilnicka E, Romano A, Szczeklik A, Testi S, Torres MJ, Wöhrl S, Makowska J. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy 2013;68:1219-32.
74. Nakamura K, Inomata N IZ. Dramatic augmentation of wheat allergy by aspirin in a dose-dependent manner. Ann Allergy, Asthma Immunol. 2006;97:712-3.
75. Marino O, Casolaro V, Meliota S, Stellato C, Guidi G, Marone G. Inhibition of histamine release from human FceRI+ cells by nimesulide. Agents Actions. 1992;36 (Suppl 2)::C311-4.
76. Matsukura S, Aihara M, Sugawara M, Kunimi Y, Matsuki M, Inoue Y, Kambara T, Ikezawa Z. Two cases of wheat-dependent

anaphylaxis induced by aspirin administration but not by exercise. Clin Exp Dermatol. 2010;35:233-7.
77. Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol Rev. 2004;56:387-437.
78. Takahashi, A, Nakajima K, Ikeda M SS. Pre-treatment with misoprostol prevents food-dependent exercise-induced anaphylaxis (FDEIA). Int J Dermatol. 2011;50:233-40.
79. Wang XS, Lau HYA. Prostaglandin E2 potentiates the immunologically stimulated histamine release from human peripheral blood-derived mast cells through EP1/EP3 receptors. Allergy. 2006;61:503-6.
80. Feng C, Beller EM, Bagga S, Boyce J a. Human mast cells express multiple EP receptors for prostaglandin E 2 that differentially modulate activation responses. Blood. 2006;107:3243-50.
81. Kuehn HS, Gilfillan AM. G protein-coupled receptors and the modification of FcεRI-mediated mast cell activation. Immunol Lett. 2007;113:59-69.
82. Hughes PJ, Holgate ST, Church MK. Adenosine inhibits and potentiates IgE-dependent histamine release from human lung mast cells by an A2-purinoceptor mediated mechanism. Biochem Pharmacol. 1984;33:3847-52.
83. Kim SH, Nam EJ, Kim YK, Ye YM, Park HS. Functional variability of the adenosine A3 receptor (ADORA3) gene polymorphism in aspirin-induced urticaria. Br J Dermatol. 2010;163:977-85.
84. Kim S-H, Kim Y-K, Park H-W, Kim S-H, Kim S-H, Ye Y-M, Min KU, Park HS. Adenosine deaminase and adenosine receptor polymorphisms in aspirin-intolerant asthma. Respir Med. 2009;103:356-63.
85. Cohen S, Barer F, Bar-Yehuda S, AP IJ, Jacobson KA, Fishman P. A(3) adenosine receptor allosteric modulator induces an anti-inflammatory effect: in vivo studies and molecular mechanism of action. Mediat Inflamm. 2014;2014:708746.
86. Leung CT, Li A, Banerjee J, Gao Z-G, Kambayashi T, Jacobson KA, Civan MM. The role of activated adenosine receptors in degranulation of human LAD2 mast cells. Purinergic Signal. 2014;10:465-75.
87. Jin X, Shepherd RK, Duling BR, Linden J. Inosine binds to A3 adenosine receptors and stimulates mast cell degranulation. J Clin Invest. 1997;100:2849-57.
88. Ramkumar V, Stiles GL, Beaven M A, Ali H. The A3 adenosine receptor is the unique adenosine receptor which facilitates release of allergic mediators in mast cells. J Biol Chem. 1993;268:16887-90.
89. Miyahara JT, Karler R. Effect of salicylate on oxidative phosphorylation and respiration of mitochondrial fragments. Biochem J. 1965;97:194-8.
90. Cronstein BN, Vandestouwe M, Druska L, Levin RI, Weissmann G. Nonsteroidal Antiinflammatory Agents Inhibit Stimulated Neutrophil Adhesion to Endothelium - Adenosine-Dependent and Independent Mechanisms. Inflammation 1994;18:323-35.
91. Feoktistov I, Biaggioni I. Adenosine A2b receptors evoke interleukin-8 secretion in human mast cells. An enprofylline-sensitive mechanism with implications for asthma. J Clin Invest. 1995;96:1979-86.
92. Hofer M, Pospíšil M, Dušek L, Hoferová Z, Weiterová L. Inhibition of cyclooxygenase-2 promotes the stimulatory action of adenosine A 3 receptor agonist on hematopoiesis in sublethally γ-irradiated mice. Biomed Pharmacother. 2011;65:427-31.
93. Ruëff F, Przybilla B, Biló MB, Müller U, Scheipl F, Aberer W, Birnbaum J, Bodzenta-Lukaszyk A, Bonifazi F, Bucher C, Campi P, Darsow U, Egger C, Haeberli G, Hawranek T, Körner M, Kucharewicz I, Küchenhoff H, Lang R, Quercia O, Reider N, Severino M, Sticherling M, Sturm GJ, Wüthrich B.. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol. 2009;124:1047-54.
94. Moneret-Vautrin D-A, Latarche C. Drugs as risk factors of food anaphylaxis in adults: a case-control study. Bull Acad Natl Med. 2009;193:351-3.
95. Jacobs RL, Rake GW, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol. 1981;68:125-7.
96. Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114:371-6.
97. Nassiri M, Babina M, Dölle S, Edenharter G, Ruëff F, Worm M. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: Evidence for direct mast cell priming. J Allergy Clin Immunol. 2015;135(2):491-9.
98. Zogaj D, Ibranji A, Hoxha M. Exercise-induced Anaphylaxis: the Role of Cofactors. Mater Sociomed. 2014;26:401-4.
99. Wang Y, Tong J, Chang B, Wang B, Zhang D, Wang B. Effects of alcohol on intestinal epithelial barrier permeability and expression of tight junction-associated proteins. Mol Med Rep. 2014;9:2352-6.
100. Nagy LE, Diamond I, Casso DJ, Franklin C, Gordon AS. Ethanol increases extracellular adenosine by inhibiting adenosine uptake via the nucleoside transporter. J Biol Chem. 1990;265:1946-51.
101. Brockow K, Kneissl D, Valentini L, Zelger O, Grosber M, Kugler C, Werich M, Darsow U, Matsuo H, Morita E, Ring J. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol. 2015;135(4):977-84.
102. Alonso M, Gomez-Rial J, Gude F, Vidal C, Gonzalez-Quintela A. Influence of experimental alcohol administration on serum immunoglobulin levels: contrasting effects on IgE and other immunoglobulin classes. Int J Immunopathol Pharmacol. 2012;25:645-55.
103. Heinz R, Waltenbaugh C. Ethanol consumption modifies dendritic cell antigen presentation in mice. Alcohol Clin Exp Res. 2007;31:1759-71.

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