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Review

Cofactors in food anaphylaxis in adults

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Key Messages

- In adults, cofactors are reportedly involved in approximately 30% of anaphylaxis reactions.
- Cofactors may influence reaction severity by either reducing the reaction threshold, increasing reaction severity, or both.
- Exercise, nonsteroidal anti-inflammatory drugs, alcohol, and sleep deprivation are the most common cofactors reported in food anaphylaxis in adults.
- Patients may be sensitive to multiple different cofactors and can require more than 1 cofactor to develop a severe reaction.
- Cofactors should be considered when taking a clinical history, to provide appropriate advice to reduce future risk.

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ABSTRACT

Around 25% to 50% of food-induced allergic reactions in adults cause anaphylaxis, and epidemiologic evidence suggests that food is the most common cause of anaphylaxis. Reaction severity is unpredictable, and patients will often experience reactions of variable severity, even to an identical exposure (both dose and allergen). A common explanation for this phenomenon has been the impact of "cofactors"—factors that might contribute to reaction severity independent of the allergen exposure. Cofactors can influence reaction severity in 2 ways: either by reducing the reaction threshold (ie, the dose needed to trigger any symptoms) so that patients have no symptoms in the absence of the cofactor and only react with the cofactor present, or by increasing reaction severity such that individuals have only mild symptoms in the absence of the cofactor, but a more severe reaction when the cofactor is present. Indeed, the same patient may have reactions with different cofactors or even need more than one cofactor to develop a severe reaction. Cofactors reportedly play a role in approximately 30% of anaphylaxis reactions in adults. Exercise, nonsteroidal, anti-inflammatory drugs, alcohol, and sleep deprivation are the most frequent cofactors reported. Routine evaluation of the possible involvement of cofactors is essential in managing patients with food anaphylaxis: in patients with a suggestive history but a negative oral food challenge, cofactors should be taken into account to provide appropriate advice to reduce the risk of future anaphylaxis.

Introduction

Around 25% to 50% of food-induced allergic reactions in adults result in anaphylaxis, and in most case series, food allergens are the most common cause of anaphylaxis.[1–3] Reaction severity is unpredictable,[4] and patients will often experience different reaction severities, even to an identical exposure (both dose and allergen). A common explanation for this phenomenon has been the impact of "cofactors"—factors that might contribute to reaction severity independent of the allergen exposure (Fig 1). Different terminologies to categorize cofactors have been proposed, for example, "intrinsic"

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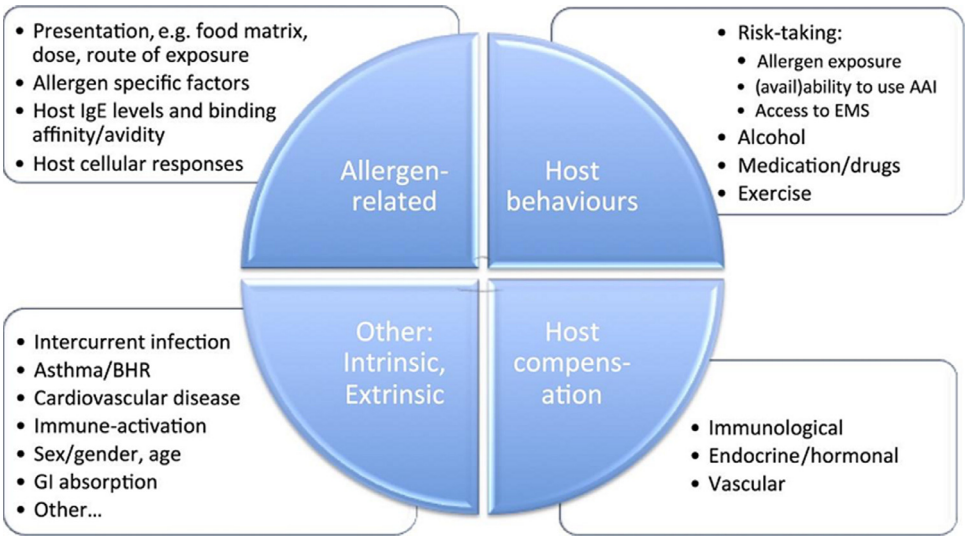

Figure 1. Factors that may modulate the severity of a food-induced allergic reaction. Reproduced from Kamdar et al[1] under Creative Commons CC BY 4.0 license. Abbreviations: AAI, epinephrine autoinjector device; BHR, bronchial hyperreactivity; EMS, emergency medical services; GI, gastrointestinal; IgE, immunoglobulin E.

cofactors which refer to those variables, which are host-dependent and typically "physiologic" (such as concomitant atopic disease, biologic sex), and "extrinsic" factors, which are related to behavior or external influences (such as intercurrent infections, exercise, alcohol consumption). In practice, this distinction is perhaps unhelpful, as frequently there is overlap between the 2 (eg, intercurrent infection acting as an immune-stimulant, alcohol impacting both risk-taking behaviors but also through a direct physiologic mechanism to increase reaction severity).[4] To address this, Niggemann et al[5] have proposed 3 categories for cofactors:

1. Augmenting factors, which might influence reaction severity through immunologic mechanisms (such as exercise or some medications);
2. Concomitant diseases, such as asthma or heart disease;
3. Cofactors, which do not seem to act through immunologic mechanisms (eg, emotional stress), although this is controversial and may be because of lack of evidence.

However, this classification has not gained widespread use and in practice, the term "cofactor" is used to describe any potential factor (independent of allergen-related variables), which might modulate the severity of an allergic reaction.

Cofactors may influence reaction severity in 2 ways (Fig 2): either (1) by reducing the reaction threshold (ie, the dose needed to trigger any symptoms) so that patients have no symptoms in the absence of the cofactor and only react with the cofactor present (Fig 3); or (2) by increasing reaction severity—such that individuals have a more severe reaction when the cofactor is present. Indeed, the same patient may have reactions with different cofactors or even need more than 1 cofactor to develop a more severe reaction. For example, in some patients, the combination of recent exposure to both a nonsteroidal anti-inflammatory drug (NSAID) and exercise or alcohol may be needed to induce food anaphylaxis, whereas either cofactor in isolation does not result in a reaction when exposed to the food allergen.[6–8] The relationship between dose and reaction severity is poorly understood; therefore, it is possible that these 2 effects may be one and the same: that in both cases, there is a reduction in reaction threshold causing people with suprathreshold reactivity to experience symptoms when they normally have none to that dose of allergen, whereas others with more typical reaction thresholds experience reactions of greater severity.[9] The mechanisms involved are complex and have diverse pathways, and might include increased intestinal permeability and increased effector cell activation (basophils and mast cells).[10,11]

Cofactors reportedly play a role in approximately 30% of anaphylactic reactions in adults vs 14% to 18.3% in children.[11–14] Most of the

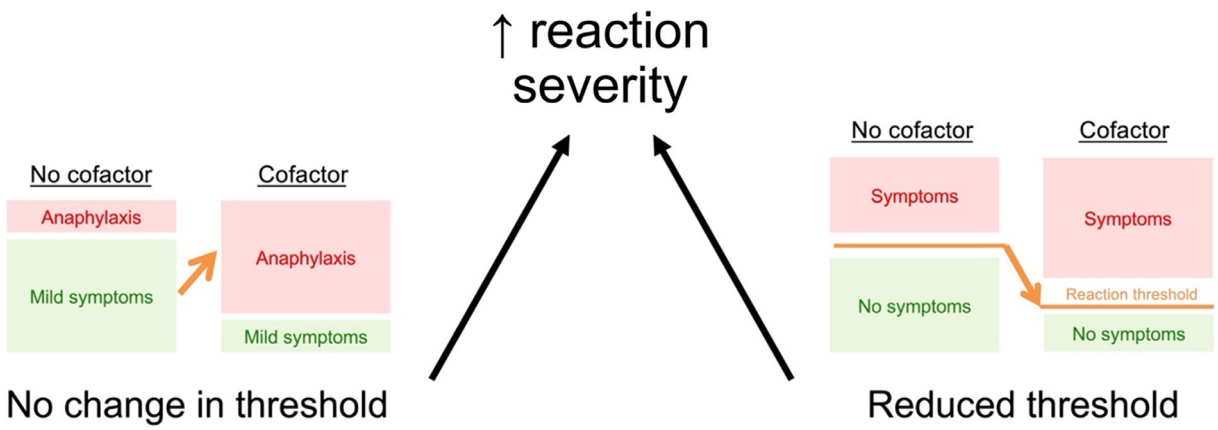

Figure 2. Cofactors can influence reaction severity in 2 ways: (1) by increasing reaction severity to the same level of allergen exposure, or (2) by reducing the reaction threshold such that the same dose of allergen causes a more severe reaction (Fig 3). Adapted from reference Niggemann et al.[5]

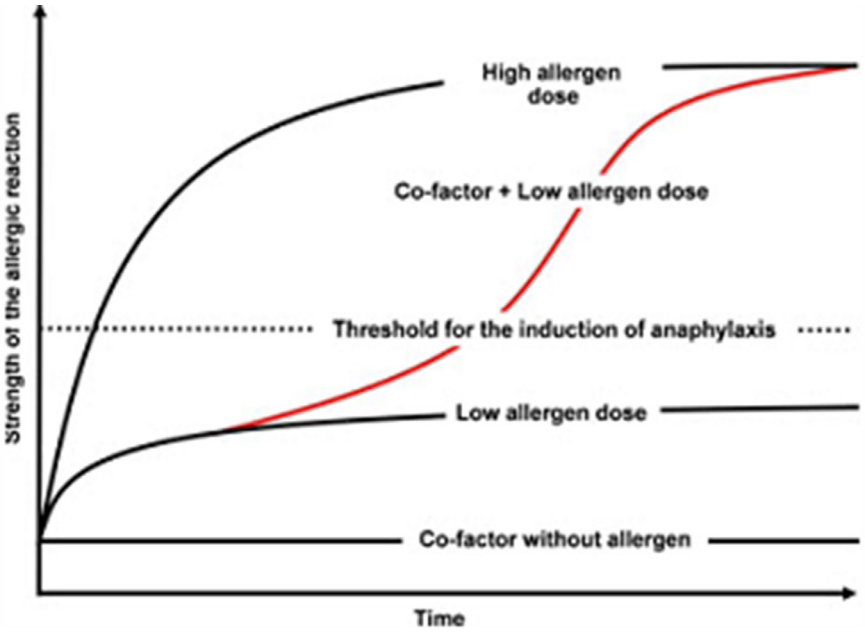

Figure 3. Cofactors may influence severity by reducing the reaction threshold. In the absence of the cofactor, exposure to the food may cause either a subclinical reaction (no symptoms) or just mild symptoms. However, in the presence of a cofactor, the reaction threshold is altered, resulting in more severe symptoms, even to "subthreshold" allergen doses. Reproduced from Wolbing et al.[11]

available data are from studies in adults. In a study of 74 adults with suspected cofactor-enhanced food allergies, anaphylaxis occurred in 85% of reactions.[15] In another study, 13% of individuals older than 16 years of age reported more severe symptoms to food after the involvement of 1 or more of the following cofactors: physical exercise (10%), alcohol consumption (5%), and use of analgesics (0.6%).[16] However, in a Spanish cohort of adults with anaphylaxis to lipid transfer proteins (LTPs), the presence of cofactors did not seem to impact severity, raising the possibility that cofactors are less relevant in LTP allergy.[8] The high frequency of cofactor-related reactions highlights the clinical impact of recognizing and including cofactors in the routine diagnostic workup. In this review, we provide an update for clinicians on the recent developments in this area.

Exercise

Exercise is the most frequently-described cofactor in food anaphylaxis, present in 10% to 20% of cases of adult anaphylaxis.[16–18] There are contradictory data as to whether exercise is more frequently a cofactor in adults compared with children.[6,17] Exercise is perhaps best described as a cofactor in food-dependent exercise-induced anaphylaxis (FDEIA), in which allergic symptoms only appear if exercise occurs, typically 1 to 4 hours after consumption of the culprit food. Food-dependent exercise-induced anaphylaxis is most typically described for wheat (wheat-dependent exercise-induced anaphylaxis [WDEIA]) in which there is an association with immunoglobulin E (IgE)–sensitization to omega-5-gliadin.[19,20] Individuals typically consume the food without symptoms, but then experience anaphylaxis if they subsequently exercise in the next 2 to 4 hours. It is now clear that even nonintensive exercise (such as walking at a normal pace) may be sufficient to elicit symptoms.[21]

Separately, exercise is also reported as a cofactor for more conventional food allergies aside from FDEIA. This phenomenon has best been described in the context of food allergy desensitization (in which individuals who tolerate a specific dose of allergen unexpectedly experience symptoms in the context of exercise around the time of allergen exposure[4]) but has also been reported for peanut allergy in the context of a randomized controlled trial.[22] Of note, in the latter study, exercise reduced reaction threshold but did not seem to impact severity.[23]

Classically, these 2 different phenotypes of exercise-associated anaphylaxis have been considered to be distinct entities. However, a recent study has challenged this: Christensen et al[20] reported that 26/71 (37%) of adults with WDEIA who at food challenge—in the lack of exercise—nevertheless reacted to very high doses of wheat. On the basis of these data, the authors suggest that many individuals with WDEIA tolerate normal levels of wheat ingestion at rest only because their clinical reaction thresholds are much higher than typical serving sizes. With exercise, the reaction threshold drops significantly, resulting in reactions to more normal portion sizes of wheat.

The mechanism(s) by which exercise might have this effect is unclear. Most studies have been undertaken only in patients with WDEIA. One hypothesis is that exercise induces activation of tissue transglutaminase, resulting in the formation of large ω-5 gliadin/tissue transglutaminase complexes that facilitate ω-5 gliadin–IgE binding. Nevertheless, no direct evidence of this phenomenon has been found in patients with WDEIA.[24] Alternatively, exercise might increase allergen absorption across the gut, impacting the reaction threshold.[10,25] Whereas this has been observed in some murine models of food allergy,[26,27] a recent study in healthy human volunteers did not find that exercise affects the absorption of gliadin.[28] This suggests that any such phenomenon might be limited to only those with WDEIA. In this respect, it is interesting to note that there is a single report of the gut microbiome composition being different in patients with WDEIA compared with healthy controls.[29] A further hypothesis is that in some individuals, redistribution of blood flow during exercise might result in an ischemia/reperfusion cycle that causes epithelial damage,[30,31] and thus, increases allergen absorption. Some authors have further suggested that as a consequence, food allergens are transported away from the gut mucosa (in which resident mast cells [MCs] tolerate them) to other tissues (eg, skin or skeletal muscle) in which MCs with a nontolerogenic phenotype react.[32] However, to date there is no experimental evidence for this.

Exercise may have a direct action on effector cells such as MCs. Physical exercise increases plasma osmolarity[33] and this could explain why some individuals develop exercise-induced anaphylaxis

(independent of exposure to a known allergen).[34] Barg et al[35] reported that patients with FDEIA may be more sensitive to exercise-induced changes in plasma osmolarity compared with controls. However, high-intensity exercise is needed to observe this impact on plasma osmolarity, whereas typically, patients with FDEIA have issues even with nonintensive exercise. Some in vivo studies have revealed an increase in histamine release (HR), with or without an increase in basophil count after exercise.[36,37] Again, however, this seems to require high-intensity exercise and at least 1 study found an increase in HR after in vitro IgE-activation only in highly trained athletes compared with nontrained ones, although both groups were nonatopic.[38] Perhaps the presence of atopy together with the "fitness" level of a participant act as "conditioning factors" increasing the impact of exercise on basophil and MC activation. Mounting evidence supports that HR during exercise is a normal physiologic response linked to recovery.[39] Histamine acts as a vasodilator and is involved in postexercise hypotension and hyperemia.[39,40] Therefore, 1 hypothesis that may need further exploration is whether this exercise recovery system in patients with FDEIA is somehow damaged and, therefore, exercise induces "excessive" effector cell activation. Unfortunately, significant heterogeneity in experimental study design (eg, measurement times and methods, sample types, and exercise intensity/duration) preclude any clear interpretations.

Finally, another potential mechanism may be related to eicosanoid metabolism. Exercise is associated with an increase in the serum of metabolites by means of the eicosanoid pathway.[41] Different models have illustrated that prostaglandin E (PGE) 2 inhibits IgE-mediated MC activation.[42–44] Interestingly, misoprostol, a PGE1 analog, has been reported to suppress symptoms in WDEIA.[45,46] Studies have found that patients with anaphylaxis had lower baseline PGE2 serum levels, suggesting that PGE2 may protect from anaphylaxis. However, whereas Rastogi et al[47] reported that PGE2 may protect from Hymenoptera-induced anaphylaxis, Muñoz-Cano et al[48] did not find any evidence for this, at least in patients with food-induced anaphylaxis.

In summary, exercise is a common cofactor in food anaphylaxis, with evidence for both an effect on reaction threshold and increasing severity (Fig 4). However, the mechanisms involved remain unclear. The recent data from Christensen et al[7] highlight the need to exclude the potential risk of reaction from very high doses of the food allergen in patients being evaluated for FDEIA.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs constitute a heterogenous group of typically-used medications. Their main mechanism of action, despite the differences in their chemical structure, is by inhibition of the cyclooxygenase (COX) pathway.[49] Nonsteroidal anti-inflammatory drugs are reported to be a potential factor in up to 22% of cases of food-induced severe anaphylaxis, constituting a risk factor with an odds ratio (OR) greater than 11.[50] In the Mediterranean region, in which there is a relatively higher prevalence of LTP allergy, NSAIDs may be far more common as a cofactor, present in more than half of cofactor-induced food-related anaphylaxis episodes.[15,51,52]

Food-dependent NSAID-induced anaphylaxis (FDNIA) is an entity in which reactions only occur if both the food allergen and the trigger NSAID are present.[53,54] In a Spanish cohort of 328 adults with suspected hypersensitivity to NSAIDs, FDNIA was diagnosed in 16% of cases.[55] Typically, reactions occur around 1 to 2 hours after NSAID administration and food ingestion; the precise temporal relationship between food exposure and NSAID is unclear but usually occurs near each other. Such individuals are typically referred for evaluation of NSAID hypersensitivity, but negative at drug provocation in the lack of food. Trigger foods include wheat, peanut, tree nuts, seeds, vegetables, and shellfish, with wheat, plant foods, and shellfish as the most common triggers. Clues to FDNIA include IgE-sensitization to Pru p 3 and Tri a 19.

Several studies have reported that NSAIDs can also induce anaphylaxis in patients with FDEIA even though NSAIDs were not implicated in previous reactions.[56,57] The underlying mechanisms of this synergistic effect are not completely understood; 2 main theories have been proposed. One is related to an alteration of intestinal permeability by NSAIDs, leading to an increase of allergen absorption,[58] whereas the other is through a direct action of NSAIDs on effector cells. Nonsteroidal anti-inflammatory drugs have been found to induce MC activation in both human and animal models. In NSAID-exacerbated respiratory disease (N-ERD) patients, Steinke et al[59] found that aspirin-induced MC activation by measuring calcium influx and PGD2 release. Interestingly, patients with N-ERD have decreased expression of the PGE2 receptor 2 subtypes (EP2) that may reduce the capacity of PGE2 to exert anti-inflammatory action.[60] Indeed, N-ERD is associated with decreased production of PGE2.[61] Pascal et al[62] reported that NSAIDs may enhance IgE-mediated

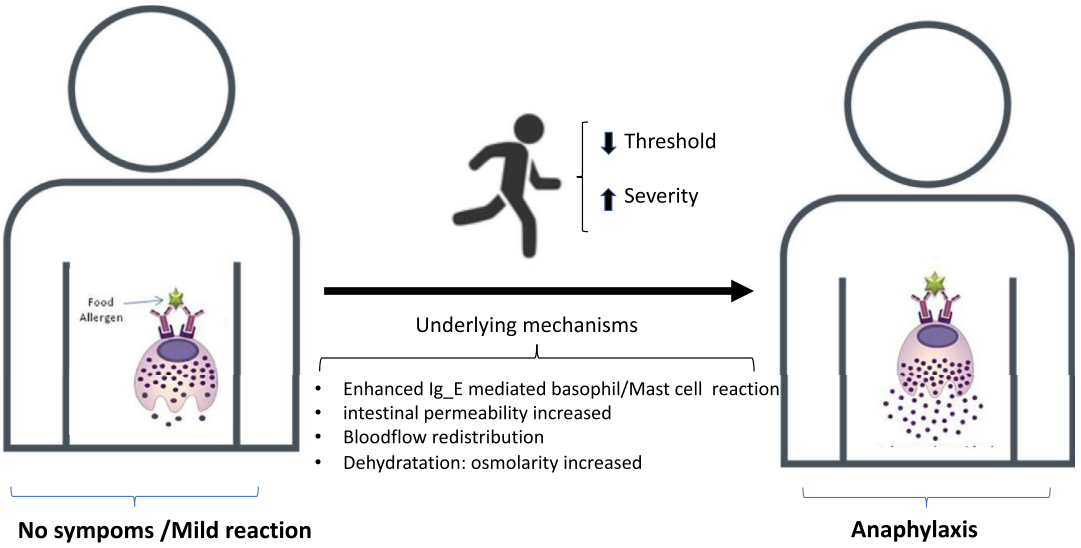

Figure 4. Exercise (both intense such as jogging or cycling, but also moderate exercise including walking in some individuals) acts as a cofactor in food anaphylaxis, decreasing the threshold of allergen and increasing the severity of the reaction. Its effect on intestinal permeability, blood flow redistribution, and effector cells in allergy response (MC, basophils) can be some of the underlying mechanisms. IgE, immunoglobulin E.

reactions in patients with food allergy through a COX1-dependent mechanism. The authors found that activation of patient-derived basophils by Pru p 3 (peach lipid transfer protein) was enhanced by aspirin, an effect that was not observed with valdecoxib, a selective COX-2 inhibitor. This is consistent with an older study that found that several chemically-unrelated NSAIDs (nonselective COX inhibitors) enhanced ragweed-induced HR from human leucocytes (almost certainly basophils).[63] Clinical challenges also have revealed the potentiation of symptoms with aspirin but not preferential COX-2 inhibitors in FDEIA.[56,64] Other reports in the literature are suggestive of a protective role for PGE2 in anaphylaxis.[47,48] Muñoz-Cano et al[48] also found decreased expression of EP4 (anti-inflammatory) and increased expression of EP3 (proinflammatory) receptors in basophils, in patients with FDNIA, and food-induced anaphylaxis; however, they could not distinguish between these 2 phenotypes on the basis of these observations. Together, these data suggest that eicosanoid metabolism may be involved in the pathophysiology of anaphylaxis, and therefore, anything inhibiting PGE2 production (such as NSAIDs) may exacerbate reaction severity.

Further evidence for a difference in the pathogenesis of cofactor-dependent and -independent anaphylaxis was provided by Muñoz-Cano et al,[65] who reported differences at the transcriptome level. Altered B-cell pathways, increased markers of neutrophil activation, and reactive oxygen species levels were exclusively observed in all patients with food allergy (cofactor-dependent and -independent) compared with controls. However, adenosine metabolism-related genes were differentially expressed only in FDNIA, particularly an overexpression of ADORA3.

Adenosine metabolism has been related to some NSAID-exacerbated cutaneous and respiratory diseases. ADORA3 polymorphism has been identified in patients with NSAID-exacerbated urticaria [66] and ADORA1 and ADORA2A in patients with N-ERD.[67] Cronstein et al[68–70] reported a series of studies using animal and human models exhibiting NSAIDs increase the adenosine release into the extracellular milieu. The authors hypothesized that the anti-inflammatory effects of NSAIDs are partly COX-independent, and instead mediated by adenosine. Adenosine-A3 agonists have been found to have anti-inflammatory effects in some murine models because of the inhibition of interferon gamma.[71,72] Interestingly, Pouliot et al[73] found that adenosine upregulates COX-2 expression, with a consequent increase in PGE2 production through A2A. This suggests that the inhibitory effect of the A2A receptor depends on a COX2-PGE2−EP axis. Further studies are still needed to understand the specific role of adenosine metabolism in food-induced anaphylaxis and the potential link between adenosine and PGE2 metabolism, both apparently involved in the development of FDNIA.

Alcohol

In the European Anaphylaxis Register, 3% of events were reported to be associated with alcohol.[16] In contrast, in a prospective series of accidental reactions in adults with food allergy, alcohol consumption may have been a factor in 16% of reactions.[74] Whereas alcohol may impact reactions through its effects on behavior, there are also data suggesting a direct physiological effect on MC activation and intestinal permeability.[75–77] Acetaldehyde-induced MC activation is one of the suggested mechanisms involved in alcohol-induced asthma in Japanese patients. Alcohol can have proinflammatory effects by increasing mediator (IL-6, IL-10, and interferon gamma) release and eicosanoid metabolite production, such as PGE2.[78] Another possible mechanism is the potential inhibition of adenosine uptake, at least with acute consumption.[79] Alcohol may also be able to act in combination with other cofactors: Brand et al[80] recently reported that aspirin in combination with alcohol could exacerbate skin prick wheal size in a passive cutaneous anaphylaxis model in human volunteers.

Angiotensin-Converting Enzyme Inhibitors and β-Blockers

Angiotensin-converting enzyme inhibitors (ACE inhibitors) and β-blockers are the 2 most typical medications reported to act as cofactors in anaphylaxis, in both retrospective and prospective studies.[16,18,50,81–84] However, data are conflicting, with a prospective case series of accidental allergic reactions in adults failing to identify the prescription of β-blockers, ACE inhibitors, or angiotensin receptor blockers as a risk factor for more severe reactions.[74] Some of these discrepancies may be because of confounding by indication, as many studies have not been able to disentangle the impact of the underlying reason for a prescription (eg, cardiovascular disease, age) as a potential confounder. A recent meta-analysis of 15 observational studies reported that β-blockers (OR, 2.2; 95% confidence interval, 1.3-3.8) and ACE inhibitors (OR, 1.6; 95% confidence interval, 1.1-2.2) were associated with increased severity for all-cause anaphylaxis; however, the authors were unable to adjust for underlying cardiovascular disease or differences between food and nonfood triggers.[85] In a large retrospective study of emergency presentations, ACE inhibitor prescriptions (but not antidepressants, β-blockers, α-adrenergic blockers, or angiotensin II receptor antagonists) were associated with severity after adjusting for cardiovascular disease and age.[86] It has been suggested that any impact on severity may only be apparent in individuals using both ACE inhibitors and β-blockers and of note, in a murine model of anaphylaxis, ACE inhibitors, and β-blockers act synergistically to increase IgE-mediated MC degranulation.[84]

Lipid-Lowering Drugs

Some authors have suggested that lipid-lowering drugs might be potential cofactors in anaphylaxis. These drugs increase the plasma concentration of platelet aggregation factor (PAF) by reducing PAF-acetylhydrolase (PAF-AH) activity.[87,88] Perelman et al[89] reported a significant correlation between PAF-AH activity and low-density lipoprotein levels in patients with peanut allergy. A significant correlation between PAF levels and the severity of anaphylaxis has been reported,[90] although these data are inconclusive. Further studies are needed to clarify whether this class of medication and/or levels of low-density lipoprotein are associated with severity.

Estrogens

Differences in biologic sex seem to impact the epidemiology of food-induced anaphylaxis, with a male predominance until puberty but then a skewing toward females after puberty[91–94]; this suggests a contributory role for estrogens. However, in the European Anaphylaxis Register, a slightly higher risk of more severe anaphylaxis has been noted in postpubertal males (13-56 years) compared with age-matched females.[95] One study has reported a sex difference in EIA, with a 2:1 female-to-male ratio.[96] In those at risk of recurrent anaphylaxis, an increase in anaphylaxis events around menstruation has been observed,[97,98] a phenomenon also noted in some females undergoing food allergy desensitization.

Data from in vitro studies[99–101] and animal models[102] suggest that estrogens may modulate severity, with higher levels of estrogen being associated with greater severity. This does not seem to be because of direct action on MC but rather, through an increase in vascular permeability.[102] However, these data contradict clinical observations in humans, in which the “at risk” period seems to be around the time of menstruation, a time when estrogen and progesterone levels are at their nadir. This is also consistent with catamenial anaphylaxis, in which, again, anaphylaxis events (in the absence of external triggers) are associated with menstrual bleeding.[103] Given that menstruation has been proposed as a possible cofactor in unexpected allergic reactions during food allergy desensitization,[104] the potential impact of the menstrual cycle on anaphylaxis risk needs further

evaluation because this may impact the advice given to individuals with allergy undergoing treatment in terms of dosing.

Proton Pump Inhibitors

Medications that modulate gastric pH—in particular, proton pump inhibitors (PPIs)—may lead to less effective acid inactivation of food allergens and, thus, impact allergic reactions. Murine models have revealed that PPIs increase the risks of food sensitization and anaphylaxis.[105] Recently, Vega et al[106] described 4 possible cases in which the concomitant use of PPI may have contributed to clinical reactions during milk oral immunotherapy. The impact of PPI on both threshold and reaction severity has been assessed in a randomized clinical trial in walnut-allergic individuals and is expected to report shortly (https://clinicaltrials.gov/ct2/show/NCT02552537).

Sleep Deprivation

In a randomized controlled trial in adults with peanut allergy, Dua et al[22,23] recently reported that sleep deprivation was associated with a reduction in reaction threshold (dose needed to trigger an objective reaction) and impact on severity. The mechanism by which this might occur is unclear. The authors suggest that sleep deprivation increases stress, which could affect small intestinal permeability.[107,108] Certainly, the impact of acute stress in atopic diseases such as asthma and atopic dermatitis has been described and may be because of the release of neuropeptides and neurotransmitters in the central nervous system[109]; however, data with respect to food allergy are lacking.

Conclusion

The presence or absence of cofactors may explain why some food allergens sometimes lead to anaphylaxis, whereas at other times are tolerated or only associated with mild reactions. Exercise, NSAIDs, alcohol, and sleep deprivation are the most frequent cofactors involved in food anaphylaxis in adults and probably act by decreasing the reaction threshold needed to cause a reaction and/or through poorly described mechanisms that increase reaction severity. Routine evaluation of the possible involvement of cofactors is essential in managing patients with food anaphylaxis: in patients with a suggestive history but a negative oral food challenge, cofactors should be taken into account to provide appropriate advice to reduce the risk of future anaphylaxis.

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