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Augmentation to Anaphylaxis: The Role of Aspirin and Physical Exercise as Co-factors

In recent years there has been a growth in interest in better identifying and characterizing co-factor-dependent anaphylaxis. Progress in this subject is of importance for general dermatologists, because we recognize that many of the patients with food allergy who depend on co-factors or augmentation factors, such as exercise, in fact present with chronic intermittent urticaria.

It is textbook knowledge that type I allergic reactions are induced by binding of allergens to IgE/FcεRI complexes on mast cell and basophil surfaces, initiating the release of preformed, mainly vasoactive, mediators, such as histamine. Anaphylaxis, the most severe presentation of type I allergy, can be life-threatening, and it is crucial to identify the causal substance in order best to manage the patients. To this end, it is important to be aware of a possible role of so-called co-factors or augmentation-factors, such as infections, physical exercise, exposure to acetylsalicylic acid (ASA), alcohol consumption, or menstruation (1–5).

The best-documented disease entity that includes the co-factor exercise is called wheat-dependent exercise-induced anaphylaxis (WDEIA). In WDEIA sensitization to wheat, and in food-dependent exercise-induced anaphylaxis (FDEIA), sensitization to other food, is a prerequisite for this disease. However, anaphylactic reactions occur only after consuming the food in association with physical exercise (4–6). Many of the patients with WDEIA or FDEIA present with an intermittent type of chronic urticaria that is falsely diagnosed as "only" physical urticaria. Consequently, WDEIA and FDEIA are listed in current guidelines for urticaria (7). It is important to know that some patients require more than one co-factor to elicit WDEIA/FDEIA, such as physical exercise and non-steroidal anti-inflammatory drugs, or physical exercise and menstruation (4, 8).

The diagnosis of FDEIA should be made by a combination of skin prick testing, measuring specific IgE and provocation testing of the suspected food allergen alone and in combination with physical exercise and so on. In case of WDEIA, most patients are sensitized to the wheat constituent ω-5 gliadin and many do not show IgE to the complete wheat extract (9).

Even though we understand that certain allergens, such as ω-5 gliadin, induce anaphylaxis in sensitized patients only in combination with co-factors, we still do not know enough about the underlying causes for co-factors to be functional. The current working hypotheses are: (*i*) increased gastrointestinal permeability resulting in an increased allergen uptake; (*ii*) increased serum osmolality and changes in pH facilitating effector cell degranulation; (*iii*) cross-linking of the allergens with human proteins, such as ω-5 gliadin with tissue transglutaminase resulting in aggregates with higher degranulation potential; and (*iv*) induction of endogenous endorphins with effects on mast cell activation and blood flow redistribution (10). Clearly, further analyses on this subject are more than welcome.

In this issue, Fukunaga et al. (11) investigate the direct influence of aspirin as co-factor on mast cell and basophil activation in patients with proven FDEIA or WDEIA. This is especially interesting to investigate, because non-steroidal drugs such as aspirin can also elicit urticaria or angioedema in up to 20% of patients with chronic urticaria (12). The authors investigated whether the intake of ASA leads to increased skin prick test reactions to the respective allergens or to increased rates of basophil activation *in vitro*. These investigations are useful to evaluate possible diagnostic measures and to better understand the underlying pathogenesis of FDEIA (see (*i*)–(*iv*), above).

Ten patients with proven FDEIA by skin prick test were recruited for measurement of specific IgE and provocation tests. In 4 of these patients type I allergy was seen following allergen challenge plus physical exercise, and in 7 either additional ASA pretreatment or ASA pretreatment alone was needed to provoke symptoms of anaphylaxis. The authors performed skin prick tests and *in vitro* basophil activation tests with the causative food allergens prior to and 2 h after treatment with ASA 500 mg. However, ASA pretreatment of FDEIA/WDEIA patients did not increase skin prick test results or reactivity of basophils. Yet, previous investigators were able to show augmented skin prick test reactions following aspirin intake in FDEIA patients (13–15).

For now, the authors conclude that skin prick tests and basophil activation tests are useful to detect sensitizations in FDEIA patients, but that ASA pretreatment is a useful diagnostic measure only in FDEIA provocation. Thus, even if the question of how ASA acts as co-factor of anaphylaxis has not been clarified, it is expected that the rapidly increasing knowledge in this field will soon disclose the mechanisms underlying co-factor-dependent anaphylaxis and help to better diagnose and treat these otherwise life-threatening reactions.

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Florian Wölbing and Tilo Biedermann
Department of Dermatology
University of Tübingen, Liebermeisterstrasse 25
DE-72076 Tübingen, Germany