Editorial

Of mice and men, MMXXI: Anaphylaxis

Thomas A. Platts-Mills, MD, PhD, Ryan C. Eid, MD, and Behnam Keshavarz, PhD

Charlottesville, Va

Key words: Food allergy, allergic disease, alpha-gal, gastrointestinal absorption

When Portier and Richet demonstrated in 1902 that repeated injections of a foreign substance could lead to increasingly severe reactions up to and including rapid death, they used a jellyfish toxin to immunize dogs and the Greek term ἀνάφυλαξις or non-protection. Thus there is no doubt that animal models can provide important information about these reactions and that they can be very severe. In their article in the current issue of the Journal of Allergy and Clinical Immunology, Gertie et al. present a detailed investigation of the factors influencing the severity of allergic reactions in 2 strains of mice. The data presented provide compelling evidence that the differences in reactions following oral exposure are not due to genetic differences in Toll-like receptor 4 or dedicator of cytokinesis 8, which had been proposed, and do not reflect differences between C3H/HeJ and C57BL/6 mice either in IgE responses to peanut or in the microbiome. On the other hand, they demonstrate significantly increased levels of gut absorption in the C3H/HeJ mice that correlate with their reactions to oral challenge.1

Speaking as known agnostics about the use of mouse models to study allergic disease, Gertie et al. create an opportunity to consider which aspects of anaphylaxis in mice can provide useful or even important information about the phenomenon in humans. Several criticisms of animal models of anaphylaxis are well known. In mice, the primary marker used to assess reactions is a decrease in body temperature, which has not been recognized as a useful marker of reactions in humans. In most mouse studies, all the animals are fully inbred and essentially identical genetically; thus, demonstrating differences between 2 or more strains is not comparable to reporting results on 260 outbred Homo sapiens patients.2 On the other hand, there are many questions that are difficult to approach in patients or healthy subjects, and some interesting experiments that are truly impossible. We would like to focus on 2 elements that are a challenge in our own current work. First, it would be ill-advised to propose carrying out experimental studies that include immunizing naïve human individuals if the sensitization could lead to a potentially dangerous outcome.

Second, some reactions to food, even in subjects with high-titer IgE antibodies, take 3 or more hours to occur and nonetheless can be severe. Carrying out food challenges to investigate anaphylaxis, especially when symptom onset can be delayed by as much as 4 hours, is a challenge for the investigators2 (Fig 1). Experiments in naïve mice have established that immunization through mildly abraded or tape-stripped skin can induce serum IgE antibodies, leading to sensitization of an unexposed organ such as the lungs.4 This has provided extensive background for understanding the relevance of skin exposure to the onset of peanut allergy.5 In addition, the mouse experiments have provided a solid background for the investigation of tick bites as a cause of sensitization to cetuximab and red meat.6,7 A recent series of experiments used tick saliva extracts to immunize alpha-gal knockout (AGKO) mice.5 Those studies produced high titers of IgE antibodies as well as marked increases in total IgE level. Furthermore, the mice reacted rapidly to oral challenge with pork kidney allergens. Another problem is to understand why most clinical reactions to mammalian meat in individuals with IgE to galactose-alpha-1,3-galactose are delayed.2 Gertie et al. report measurements of ovalbumin protein entering the circulation within 30 minutes after gavage. In keeping with the stronger allergic reactions, they also document greater quantities of ovalbumin in the circulation of C3H/HeJ mice than in other mouse strains, including C57BL/6. Interestingly, the recent studies of challenges of alpha-gal–sensitized mice using homogenized pork kidney reported a rapid decrease in temperature in the AGKO mice, which are on a C57BL/6 background (Fig 1). In a sense, the results of that study challenge the possibility that the C57BL/6 mice have a general difference that decreases gut absorption of foreign antigens. On the other hand, these observations in 2 different models of gut absorption using mice bring to light the difficulty of studying delayed absorption in humans or in mouse studies. This is particularly relevant to food-related exercise-induced anaphylaxis and delayed reactions to red meat.

In patients with food-dependent exercise-induced anaphylaxis, the response depends on exposure to a specific allergen followed by exercise up to 3 hours later (Fig 1).9 The interesting point here is that the most common allergen source is wheat and the relevant protein component has been shown to be omega-5-gliadin or Triticum aestivum 19. Furthermore, there is a well-known form of this condition in which sensitization to the relevant protein occurs as a result of use of a wheat-containing face cream that is applied to the skin.10 There is an interesting model of exercise in a mouse strain in which there is an associated increase in absorption of a relevant allergen.9,11 However, how it would be possible to explain the relevance of a specific wheat allergen is difficult to work out.

A significant problem with animal models of allergic disease arises because the quantities of allergen are higher than those in cases of natural exposure of patients experiencing symptoms. Clearly, there is a very wide range of sensitivity among individuals with allergy, such that some individuals with peanut allergy react to quantities of the allergen that are difficult to
measure. With delayed reactions to red meat, the patients may eat or be challenged orally with large quantities of the antigen in the form of beef or pork kidney. However, the quantity of the allergen that is present in the circulation at the time of reactions may be only a tiny fraction of the quantity eaten. In a series of experiments in Gertie et al., almost 50% of the mice either died or had a symptom score of 4 and were humanely killed. Clearly, that number implies a high dose because the mortality rate in naturally occurring episodes of anaphylaxis in patients with allergy is generally considered to be less than 1%. So, the question has to be whether it would be possible to study delays in time effects by using lower doses of allergens in the challenges.

We recognize that Gertie et al. provide important information about the basis for the severity of anaphylaxis to peanut in 2 strains of mice. In humans, however, there is a high degree of interpersonal and intrapersonal variation in the “threshold doses” of allergen needed to elicit a reaction and in the severity of symptoms observed. That is, in human subjects allergic reactions to a known allergen exposure are highly variable. There are several well-recognized factors that can influence anaphylactic responses, including alcohol, aspirin, nonsteroidal anti-inflammatory drugs, and exercise. However, in addition, there must be other factors that make human responses difficult to predict. Thus, there are major differences in both the timing and the severity of humans’ allergic reactions to food, and it is always important to keep in mind the problems that exist when investigating the mechanisms of anaphylaxis either in patients or in sensitized mice.

### References