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SCIENCE BEHIND THE NUTRITIONAL
MANAGEMENT OF THE ADVERSE REACTIONS TO FOOD

HA
HYPOALLERGENIC
DOGS
SCIENTIFIC APPROVED

INTRODUCTION

Clinical veterinarians and dermatologists are constantly faced with food and nutrition-related skin diseases. Among these, in dogs and cats, adverse food reactions (AFR) are the most common[1], which are divided into two categories: immunological (IgE mediated or not) - known as food allergy - or non-immunological adverse reactions[2, 3 and 4]

Estimations show AFRs represent 1-6% of the dermatoses found in clinical routine, of which 10-49% are (immunological) food allergies[5,6]. The precise prevalence of these dermatoses is challenging as they mimic the symptoms of different diseases, especially pruritic dermatoses, and often coexist with other allergic conditions[7]. The most frequent clinical signs in dogs with AFR are non-seasonal pruritus, chronic external otitis and seborrhea, which may come or not along with gastrointestinal manifestations[8]. Both vomit and diarrhea are reported signs in more than 20% of dogs with AFR[9]. No clear predisposition of age, breed and gender can be found to adverse food reactions in dogs[8].

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KEY NUTRITIONAL FACTORS

As trophoallergens usually are glycoproteins, the treatment and nutritional interventions principle for AFR management is based on refraining from offering these trophoallergens. Thus, dietary protein is the main nutritional factor that will be managed in these disorders, as is the offering of omega-3 to help control inflammation and modulate immune responses[7]. Other factors that, at appropriate levels, could be favorable are zinc and selenium. Zinc is an essential microelement and an important cofactor of multiple metalloenzymes and modulator of several biological functions.

Within the animal body it can be found in higher concentrations in the epidermis tissues, causing several skin diseases in dogs either in primary or secondary zinc deficiency or in response to the supplementation of this microelement[10]. Thus, adequate levels of zinc in food are important for maintaining a healthy skin. Selenium, also an essential microelement, plays an important role in hair growth, so that both its excess and its deficit are harmful. Selenium levels between 0.12 and 1.03 mg/kg of diet in dry matter, contribute to a higher hair growth rate[11].

HYPOALLERGENIC PROTEIN

HYDROLYZED SOY PROTEIN

- High digestibility.
- Low molecular weight. (proteins below 5,000 Da)
- Ideal for AFR management.

Both in dogs and cats as in humans, the gold standard diagnosis of AFR is the oral restriction-provoking test, which is based on the recurrence of the reaction manifestations after the ingestion of certain ingredients/foods, and is followed by the improvement of the signs with the use of hypoallergenic diets[7,12,13]. Usually, trophoallergens are water soluble thermostable glycoproteins with molecular weight between 10kDa and 70 kDa[14]. *Mueller et al. (2016)* conducted a bibliographic review of publications from 1985 to 2015 to find out which would be the most common allergens in dogs and cats. After finding in the literature 1674 results of this search, they have chosen the researches with relevant information and were able to conclude that for dogs from Australia, Europe and North America, the allergens that most contribute to the AFR are, by order of relevance, bovine meat, dairy products, chicken, wheat and lamb; and for cats, bovine meat, fish and chicken.

Thus, hypoallergenic diets use two main strategies for AFR management:

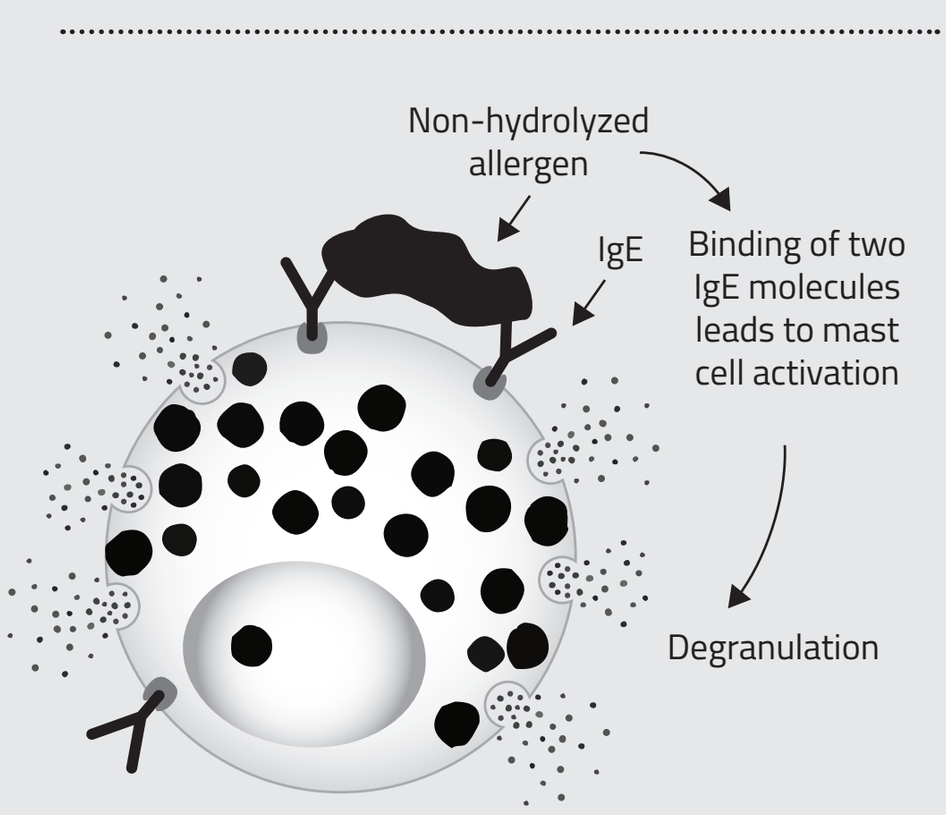
NEW SOURCE OF PROTEIN:
That the animal has never ingested and the immune system does not recognize as an allergen

HYDROLYZED SOURCE OF PROTEIN:
That is the breakdown of the protein source into smaller peptides and amino acids to reduce its molecular weight[15].

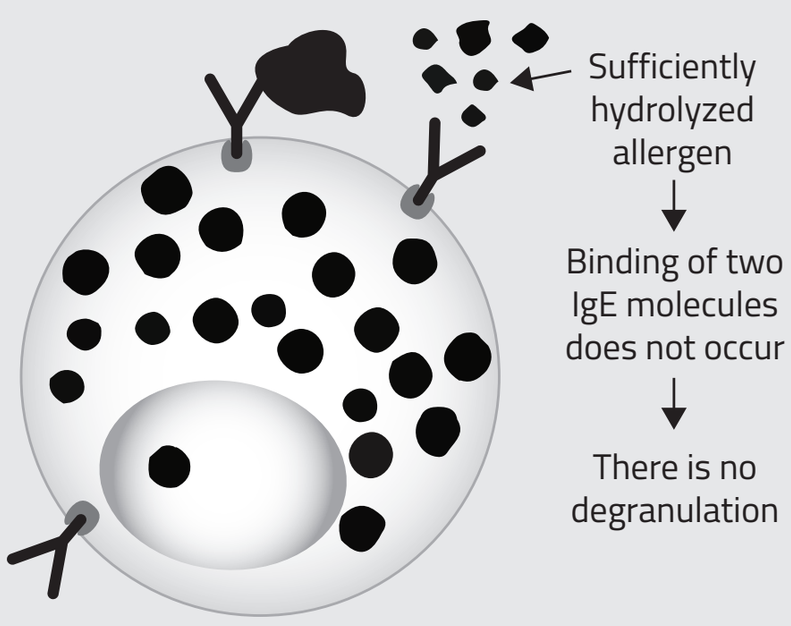
With such growth and development of the pet food market, there are several diets on the market, with a wide range of ingredients, making it challenging to use new sources of protein for the immune system[7]. Furthermore, the length of this original source of protein for gut-associated lymphatic tissue (GALT) is likely to be short if offered to an animal with increased intestinal permeability[7]. Another factor that should be considered is that many pet parent tend to give their animals treats or leftovers, and the potential for cross-protein immune reaction further reduces the options that can be used[16]. Therefore, the use of hypoallergenic diets with a source of hydrolysed protein is a strategy widely employed by veterinarians for the management of AFRs.

» The use of hydrolyzed protein sources in an appropriate molecular size (<10,000 Daltons) makes immune responses less likely to occur[7]. This is because IgE-mediated ARFs arise from the binding of food allergens (i.e., glycoproteins) to two nearby IgE molecules, causing the activation and degranulation of mast cells, thus initiating the allergic response[4]. To cause this mast cell activation, these proteins are usually larger than 10,000 Daltons[7, 17] (Figure 1), so the hydrolysis of intact proteins into smaller fragments hinders this binding to two IgE molecules[18]. Additionally, the hydrolysis of the protein changes its structure, so that this peptide is not recognized by the immune system even though it has already been sensitized to the intact form of the protein[17]. Thus, the use of hypoallergenic diet using hydrolyzed protein has been shown to be efficient for the diagnosis and management of AFR[1].

Figure 1. Adapted illustration from Cave (2006) showing the requirements for mast cell activation.



A. Mast cells are activated by binding intact protein to two nearby IgE molecules, causing degranulation and release of inflammatory compounds.



B. Hydrolyzed protein in adequate size (<10,000 Daltons) cannot bind to two IgE molecules at the same time, not causing mast cell activation and degranulation.

The digestibility of hydrolyzed protein is usually greater than its intact form, which also contributes to the reduction of its allergenicity, since when portions of intact protein are not digested, they remain for a longer period in the intestinal lumen and the immune system may initiate an adverse response to the food[7,17]. The increased digestibility of hydrolyzed protein causes a large part of it to be absorbed and those that still remain in the intestinal lumen have low molecular weight, hindering IgE activation. It is worth mentioning that hypoallergenic commercial diets that use hydrolyzed protein are also comprehensive and balanced for the nutritional needs of adult dogs, and can be used continuously if the animal is diagnosed with AFR[7,17,19].

OMEGA-6 and 3
EPA/DHA

Schizochytrium sp.
SEAWEED + FISH OIL

- Anti-inflammatory levels.
- Scientifically proven.

Besides being excellent sources of energy for the body, fats play other important roles, such as enabling the absorption of liposoluble vitamins and providing important essential fatty acids that act as precursors of inflammatory mediators, called eicosanoids, in addition to being incorporated into the cell membrane, changing its fluidity [20]. Thus, fat is essential in the diet of dogs and cats to provide essential fatty acids (EFA), which belong to two distinct families: omega-6 and omega-3.

The omega-6 fatty acids start from linoleic acid (LA), while the omega-3 fatty acids from α-linolenic (ALA). Linoleic acid consists of 18 carbons and has two double bonds (18:2 n-6), while α-linolenic acid has 18 carbons and three double bonds (18:3 n-3). Both can be converted in the body into other long chain polyunsaturated fatty acids by means of enzymatic reactions[20,21]. Linoleic acid can be metabolized into other fatty acids of the omega-6 family, such as γ-linolenic acid, γ-linolenic dihomo and arachidonic acid; just as α-linolenic acid can be metabolized into other fatty acids of the omega-3 family, such as eicosapentaenoic (EPA) and docosahexaenoic (DHA). However, during this metabolism, Ω-3 and Ω-6 compete for the same enzymes and metabolic pathways, although the end product is different, and due to the position of the first double bond in the carbon chain, the conversion of a fatty acid from the Ω-3 into Ω-6 family and vice versa is not possible, which explains how essential both are[20]. Thus, the effects of these fatty acids on the body will be influenced both by their absolute amounts in the diet and the relationship between Ω-3 and Ω-6.

In dogs, the conversion rate of linoleic and α-linolenic acids into their respective fatty acids is controlled by the Δ-6-desaturase enzyme. As this enzyme has greater specificity to the Ω-3 fatty acids, smaller amounts of these fatty acids produce the same amount of products derived from Ω-6[22], which means that there should be a higher proportion of linoleic acid than α-linolenic acid from the diet. Δ-6-desaturase of dogs can convert the linoleic acid supplied into arachidonic acid to achieve the minimum nutritional requirements. Still, adult dogs can also convert it, but into small rates, α-linolenic into EPA and DHA, causing its inclusion in the diet to be important[23].

The supplementation of essential fatty acids and the manipulation of their amounts in the diet seem to be effective in the treatment of some conditions, since they

» change the relationship of these fatty acids in the skin and other tissues. As previously mentioned, fatty acids are precursors to eicosanoid synthesis, which are involved in inflammatory reactions, immunoregulation and proliferation of epidermis cells. Ω-3 and Ω-6 produce different eicosanoids from different families, and the metabolism of Ω-3, especially the EPA, produces mediators with weaker inflammatory activity than those produced by Ω-6[19]. Therefore, for a better performance of these fatty acids, it is important that they are supplied in an optimum ratio and through a high quality source. Seaweeds synthesize large amounts of Ω-3, causing fish that live in these waters and feed on these algae to have high amounts of Ω-3 in their tissues[19].

The main function of α-linolenic is to act on the synthesis of EPA and DHA, which are incorporated into the cell membrane and serve as precursors for eicosanoids with lower inflammatory power - therefore often called components with "anti-inflammatory" effect[20]. Conditionally, although EPA and DHA are essential fatty acids in some life stages, for adult dogs the minimum nutritional requirement has not yet been established by the NRC (2006)[24]. IgE-associated skin changes, such as AFR, are the most likely to positively respond to dietary changes related to essential fatty acids. Studies in dogs suggest that the Ω-3 supplementation helps to reduce inflammatory and allergic reactions seen in skin conditions, as well as contribute to the improvement of pruritus and skin and hair characteristics.[19,24–27]. Consequently, they are essential components in the management of AFR.

ELIMINATION DIET

As previously mentioned, the gold standard diagnosis of ARF is the oral restriction-provoking test, i. e., the observation of a clinical improvement of the patient after the use of an elimination diet (with a new or hydrolyzed protein source), with the subsequent worsening of the condition after the use of the original diet[7,12]. The pet should slowly be switched to an elimination diet and remain on it for at least 5 weeks; diagnostic sensitivity increases if the elimination diet is provided for a period of 8 weeks. After this period, the provocation with the previous diet must occur for a maximum of 14 days and must be followed by provocation with suspicious sources so that the allergen ingredient is detected[7,28]. After the diagnosis of the trophoallergen, the pet should resume the elimination diet and remain with it continuously.

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