Immunologic responses against hydrolyzed soy protein in dogs with experimentally induced soy hypersensitivity

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Objective—To assess whether dogs with experimentally induced type I hypersensitivity against soy protein would respond to soy hydrolysate and develop cutaneous or gastrointestinal tract reactions after intradermal and oral challenge exposure.

Animals—12 naïve Beagle pups (9 sensitized and 3 control dogs).

Procedure—9 dogs were sensitized against soy protein by administration of allergens during a 90-day period. After the sensitization period, serum concentrations of soy-specific IgE were determined and an intradermal test was performed to confirm the dogs were sensitized against soy protein. An intradermal challenge test and an oral challenge test with native and hydrolyzed soy protein were conducted on 6 sensitized and 2 control dogs.

Results—High serum concentrations of soy-specific IgE and positive results for the intradermal test were observed for the 9 sensitized dogs after completion of the sesitization process. Sensitized dogs challenge exposed with hydrolyzed soy protein had a reduced inflammatory response after intradermal injection and no clinical response after an oral challenge exposure, compared with responses after intradermal and oral challenge exposure with native soy protein.

Conclusions and Clinical Relevance—Soy-sensitized dogs did not respond to oral administration of hydrolyzed soy protein. Thus, hydrolyzed soy protein may be useful in diets formulated for the management of dogs with adverse reactions to food. (*Am J Vet Res* 2006;67:484–488)

Food hypersensitivity is defined as an immunologic reaction against a food component or a food additive.[1] In dogs, clinical signs include gastroenteritis, recurrent bacterial dermatitis, pruritus, otitis, and urticaria.[2] Currently, homemade elimination diets are considered the standard for the diagnosis of food hypersensitivity and management of affected dogs. However, these diets may be inconvenient to prepare and contain improperly balanced amounts of nutrients.[3]

Commercial prepared formulations used for the diagnosis of adverse reaction to food and management of affected dogs include diets containing a novel protein source to which a dog has not been exposed or diets containing low–molecular-weight hydrolyzed proteins. Hydrolysis of proteins would destroy antigenic epitopes and lower the molecular weight of peptides to below the antigenic threshold.

In humans, food allergens are mostly glycoproteins with molecular weights ranging from 18 to 36 kd.[4] Hydrolyzed proteins are effective for children allergic to cow milk[5] and could be an option for use in the diagnosis of food hypersensitivity and management of affected dogs.[6] Few clinical studies[7–10] have been conducted in dogs with naturally developing food allergy to evaluate the usefulness of hydrolysate-based diets in the diagnosis of adverse food reactions; however, initial results for those studies are encouraging.

Soy hydrolysates are produced from the breakdown of isolated soy protein. They are highly digestible with a typical molecular weight of approximately 12 kd. They are used extensively in veal calves to prevent intolerance to milk replacers.[11] Analysis of results of preliminary studies[7,a] suggests that soy hydrolysates would have a reduced ability to induce type I hypersensitivity responses, even in dogs that are hypersensitive to soy protein.

The primary objective of the study reported here was to assess whether dogs with experimentally induced type I hypersensitivity against soy protein would develop cutaneous or gastrointestinal tract reactions when challenge exposed to hydrolyzed soy protein. To achieve that objective, we had to induce hypersensitivity against soy in naïve Beagle pups.

Materials and Methods

Animals—Twelve naïve Beagles (3 males and 9 females) from 3 litters were enrolled in the study at birth. Dogs were allocated into 3 groups (4 dogs/group); in each group, 3 dogs were experimentally sensitized against soy protein and 1 dog served as a control animal. Dogs were allowed to suckle their respective dam for the first 6 weeks after birth. Dogs were then weaned and fed a commercial dry, expanded diet that did not contain soy protein.[b] Guaranteed analysis for the food revealed that it contained 32% protein, 20% fat, 9% moisture, 7.5% minerals, and 2.5% crude fiber. All dogs were fed twice daily and had ad libitum access to water. Dogs were housed in the kennel of the Facultat de Veterinària, Universitat Autònoma de Barcelona. All experimental procedures were approved by the Animal Research Ethical Committee of the University of Barcelona.

Sensitization procedure—Dogs were sensitized in accordance with a protocol described elsewhere,[12] with a few modifications to doses and sites of injections. Beginning when the 9 dogs in the sensitized group were 1 day old, they were administered SC injections of 2 µg of isolated native soy protein[c] diluted in 0.2 mL of saline (0.9% NaCl) solution and 0.2 mL of alum adjuvant[d] on days 1, 22, 29, 50, 57, 78, and

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85 (first day of injections was designated as day 1). Injections were administered in the axillary regions of each sensitized dog. Control dogs were administered SC injections that contained only 0.2 mL of alum adjuvant on the same days. Beginning 30 days after completion of the sesitization protocol (day 115), booster inoculations of 20 µg of isolated soy protein in alum were administered SC on alternate months throughout the remainder of the study.

All 12 dogs were vaccinated by administration of an attenuated vaccine against distemper-hepatitis-parvovirus[e] on day 21, and an attenuated vaccine against distemper-hepatitis-leptospirosis-parvovirus[f] was administered to all dogs on days 49 and 77.

Serum concentrations of soy-specific IgE—Sera were obtained from sensitized and control dogs on days 29, 57, and 85. Circulating concentrations of soy-specific IgE were determined by use of an enzyme-labeled immunodot assay.[g] Briefly, 0.5 mL of serum diluted 1:2 with Tris–HCl buffered saline (10mM Tris; 150mM NaCl; pH, 7.4) solution was incubated in nitrocellulose strips at 23°C for 18 hours. After addition of antibody (horseradish peroxidase-labeled monoclonal anti-canine IgE), strips were incubated for an additional 2 hours. Strips were then washed with Tris–HCl buffered saline solution and developed by use of 4-chloro-1-naphtol and 3% H_2O_2. Intensity of blue dots on the strips was measured by use of an optical densitometer.[h]

Intradermal testing—Intradermal testing was conducted twice during the sensitization period. The first test was conducted on day 1 before beginning the injections, and the second test was conducted on day 85 after completion of the injections. An aliquot (40 µL) of various dilutions (1, 10, and 100 µg/mL) of native soy protein was injected ID in the ventral area of the abdomen, and wheals induced were measured 20 minutes later. Histamine[i] (25 µg/mL) was used as the positive control injection, and diluent (saline solution) was the negative control injection. To improve visibility of the perimeter of wheals, a 2% solution of Evans blue dye (0.2 mL/kg) was injected, IV, 30 minutes before the start of each test.

Area of each wheal was measured by applying a piece of acetate tape over the reaction site, which enabled investigators to draw the outline of the wheal by use of indelible ink. Wheal areas were subsequently calculated by use of computer-assisted image analysis.[j]

Challenge testing—After the induction of sensitivity against soy was confirmed on the basis of results of intradermal testing and measurement of soy-specific IgE concentrations, responses to intradermal and oral challenge exposure to native and hydrolyzed soy proteins were compared. On the basis of their stronger skin responses, 6 of 9 sensitized dogs (1 male and 5 females) were selected for this part of the study. Two of the 3 control dogs (both females) were also randomly selected for testing.

One month after completion of the sensitization procedure, an intradermal challenge test was performed in the 8 dogs (6 sensitized and 2 control dogs) selected for use in this part of the study. Dogs were 4 months old at the time of the intradermal challenge test. Three concentrations (1, 10, and 100 µg/mL) of hydrolyzed[k] soy protein and native soy protein were injected, ID, in the abdominal area of the sensitized and control dogs. Wheal areas were measured as described previously, and surface areas were compared.

A preliminary oral challenge test was performed on the 8 selected dogs when they were 12 months old. However, we did not detect responses in any of the dogs after challenge exposure with native soy protein. On the basis of the results of this preliminary test and results of another study,[13] we decided to wait until dogs were 2 to 2.5 years old to repeat the oral challenge test. During this period, booster inoculations of isolated soy protein (20 µg) were administered on alternate months, as described previously. Moreover, intradermal tests and determinations of soy-specific IgE concentrations were performed several times during the study to monitor each dog's responses; the results obtained throughout this period were similar to those obtained initially after the sensitization period. During the 1- to 1.5-year period between the preliminary oral challenge test and the subsequent oral challenge test, dogs were fed a diet that did not contain soy protein.[b]

The oral challenge test was conducted by use of a crossover design. The 8 dogs were randomly distributed into 2 groups, each of which consisted of 1 control and 3 sensitized dogs. Dogs were challenge exposed by use of oral administration of native and hydrolyzed soy protein. There was a minimum washout period of 2 weeks or until complete resolution of any clinical signs related to the challenge exposure between subsequent challenge exposures. During the washout period, dogs were fed the same diet that did not contain soy protein.[b] Dogs were housed separately 1 week before starting the first oral challenge test. They were housed separately the first week of the washout period, and then all dogs of the same group were housed together during the second week of the washout period. Dogs were monitored by a veterinarian the day before starting the oral challenge test to ensure they had a typical appetite and did not have diarrhea or vomiting. Food was withheld from dogs on the day before and the day of the oral challenge test.

On the day of a challenge exposure, soy isolate or soy hydrolysate was weighed and mixed with water to form a slurry, which was placed in syringes (1 syringe/dose) by laboratory personnel. Six doses (0.25, 0.5, 1, 2, 4, and 10 g) of each soy protein were prepared for each dog; thus, the total dose that could be administered to each dog was 17.75 g.

A veterinarian orally administered the protein to each dog as a bolus. Challenge exposure was initiated at the lowest dose (0.25 g). Subsequent doses were administered in increasing order at intervals of 20 to 30 minutes. After administration of a dose, dogs were monitored to detect vomiting, diarrhea, signs of abdominal pain, pallor of the oral mucosa, lethargy, pruritus, and erythema. When an adverse effect was observed during the test, the clinical signs were recorded and the challenge test stopped. When no adverse effects were evident after 20 to 30 minutes, the subsequent dose was administered. Dogs were examined 3 and 5 hours after completion of the oral challenge test, and fecal scores were monitored 3 times/d for the next 5 days. Feces were scored on a scale from 1 (liquid diarrhea) to 5 (hard and dry feces), with a score of 4 being optimal. During the week after the oral challenge test, a complete physical examination was performed daily and any abnormalities recorded. Body weight was recorded at weekly intervals.

Data analysis—Results were expressed as mean ± SEM. Differences between means were tested by use of Student's *t* test to detect significant differences. Significance was designated at values of $P \leq 0.05$.

Results

Sensitization procedure—Inoculation with native soy protein induced naïve Beagle dogs to produce high concentrations of soy-specific IgE. Not all dogs produced soy-specific IgE at the same rate, but all dogs had high concentrations of soy-specific IgE after completion of the 3-month sensitization period (**Table 1**). During the sensitization period, concentrations of soy-specific IgE increased in most of the dogs, but the rate differed depending on the genetic disposition of each

dog. Some dogs only reacted after the first administration of soy but did not subsequently develop high concentrations of soy-specific IgE. For this reason, some investigators will only use dogs that are high IgE responders. Soy-specific IgE concentrations were not detected in control dogs throughout the study period.

Soy-specific IgE concentrations may fluctuate over time, and in some dogs, we detected soy-specific IgE concentrations after the first or second month of inoculation but were not able to detect them subsequently. The immunodot test was always performed in accordance with the same conditions and same reactive batch, so we suggest that the observed fluctuations for soy-specific IgE concentrations were attributable to immunologic aspects of each dog, rather than as a result of the method used to detect soy-specific IgE concentrations.

All dogs included in this study were subjected to intradermal testing by use of ID injections of 3 concentrations of native soy protein on the first day after birth, and no skin reactions were observed in the dogs at that time. However, intradermal testing was repeated after completion of the sensitization period and consistently yielded positive results in all sensitized dogs, as evidenced by formation of a wheal and a dose-response relationship. Area of the wheal induced by ID injection of native soy protein (100 µg/mL) was 140.2, 96.4, 74.4, 55.3, 57.2, 58.5, 107.6, 82.5, and 122.3 mm^2 for dogs 1 through 9, respectively. In control dogs, results of intradermal tests were always negative.

Intradermal challenge testing—After completion of the sensitization procedure, the 6 dogs that had the strongest skin reactions (ie, dogs No. 1, 2, 3, 6, 7, and 9) were selected for use in the intradermal challenge testing. On the basis of the soy-specific IgE concentrations detected for these 6 dogs (Table 1), we did not detect a significant correlation between serum soy-specific IgE concentrations and skin inflammatory reaction induced by ID injection of native soy protein.

One month after completion of the sensitization procedure, intradermal testing was performed in dogs to compare the response between the native and hydrolyzed soy protein. Areas of the wheals after ID injections of native and hydrolyzed soy protein were compared. Injection of hydrolyzed soy protein induced an inflammatory response that was approximately half the response detected after injection of native soy protein. Mean ± SEM area of the wheal after injection of hydrolyzed soy protein at the 3 concentrations (1 µg/mL, 29.9 ± 5.4 mm^2; 10 µg/mL, 33.0 ± 7.1 mm^2; and 100 µg/mL, 75.7 ± 11.8 mm^2) was significantly less than the areas after injection of native soy protein (1 µg/mL, 43.2 ± 4.9 mm^2; 10 µg/mL, 56.9 ± 5.3 mm^2; and 100 µg/mL, 98.4 ± 13.6 mm^2). No skin reaction was observed in control dogs after ID injection of native or hydrolyzed soy protein.

Table 1—Titers for soy-specific IgE in serum samples obtained from dogs at various stages of a sensitization procedure, as determined by use of an enzyme-labeled immunodot assay.

Dog	Day 29*	Day 57*	Day 85*
1	ND	47	43
2	ND	3	8
3	1	16	9
4	ND	16	20
5	ND	ND	2
6	ND	11	5
7	3	6	18
8	ND	22	19
9	ND	ND	20

Values reported are the number of optical density units.
*Day 1 was the first day of the immunization procedure.
ND = Not detected.

Oral challenge testing—Definitive oral challenge testing was conducted approximately 2 years after the sensitization procedure. At that time, for the 6 selected sensitized dogs, 3 still had high concentrations (dogs No. 1, 7, and 9 with 49, 28, and 29 optical density units, respectively) of soy-specific IgE, 2 had low concentrations (11 and 14 optical density units for dogs No. 3 and 2, respectively) of soy-specific IgE, and 1 (dog No. 6) had undetectable concentrations of soy-specific IgE.

The 3 sensitized dogs with the highest concentrations of soy-specific IgE had gastrointestinal reactions that developed rapidly after oral administration of native soy protein. Dog No. 1 reacted after administration of the initial dose of 0.25 g of native soy protein; it vomited twice (5 and 15 minutes, respectively) after oral ingestion. Dog No.1 also had diarrhea (fecal score, 1) and developed pruritus and erythematous pododermatitis during the first week after challenge exposure. Dog No. 7 had soft feces (fecal score, 3) 10 minutes after ingestion of 0.5 g of native soy protein, whereas dog No. 9 had diarrhea (fecal score, 2) during the day after oral administration of 17.75 g of native soy protein. All 3 of these dogs recovered without treatment. The other 3 sensitized dogs (ie, dogs No. 2, 3, and 6) did not have evidence of clinical reactions following oral administration of native soy protein.

None of the 6 sensitized or 2 control dogs had clinical signs or reactions after oral challenge exposure with hydrolyzed soy protein. Each of these dogs was administered the 6 doses (total of 17.75 g of hydrolyzed soy protein).

Discussion

On the basis of results for studies in humans,[5] calves,[11] and dogs,[7–10] diets formulated with protein hydrolysates appear to have promise for use in the diagnosis of adverse reactions to food in companion animals and management of affected animals. By enzymatically breaking the protein down into smaller peptide fragments, it becomes intrinsically less allergenic and more digestible. This latter point is probably of great importance because dietary proteins that are properly digested prior to contact with the gastrointestinal mucosa will not activate the immune system.[9,11]

However, additional studies are required to document the benefits of protein hydrolysates in the management of adverse reactions to food. The main objective of the study reported here was to assess whether soy-sensitive dogs could recognize soy hydrolysate when challenge exposed intradermally and orally.

Sensitization of dogs against native soy protein and characterization of the immune response that

developed were the first steps of the study. In another study,[14] a colony of inbred dogs that were high producers of IgE was used as a means for evaluating hyperreactivity against pollens or foods. In the study reported here, naïve Beagles were successfully sensitized; they had high concentrations of soy-specific IgE and induced cutaneous inflammatory responses after the 3-month sensitization process.

To determine whether experimental sensitization against food allergens was accompanied by clinical signs after oral exposure to a diet containing the allergen, a clinical trial was performed 7 to 8 months after the sensitization process. In this initial trial, no clinical signs were observed after oral ingestion of any of the tested diets. We hypothesized that larger amounts of protein were necessary to induce clinical signs. Moreover, as has been reported in another study,[15] the dogs were probably not old enough to sufficiently permit development of a clinical response (ie, immunologically immature). For these reasons, we decided to repeat the oral challenge test in adult sensitized dogs, and the 6 dogs with the highest reactivity were selected for use.

The sensitization procedure induced a high rate of hypersensitivity against native soy protein and allowed us to compare in vivo responses obtained by use of hydrolyzed soy protein. This is a good method for evaluating allergies (immunologic response), but it cannot be used to predict intolerance reactions (nonimmunologic response). In the study reported here, an in vitro IgE test was used to confirm success of the sensitization procedure. In vitro tests are not useful to diagnose a food allergy; however, the immunodot test was used as a method to quantify soy-specific IgE concentrations in sensitized dogs in which IgE production was stimulated by SC injections of soy protein.

It is important to highlight that soy hypersensitivity was induced by SC injections of soy protein in the study reported here. This is not a physiologic sensitization for the development of food allergies. This could possibly explain the lack of a positive reaction after oral challenge exposure when dogs were 1 year old and in some dogs (3 of 6 sensitized dogs). It is probable that simultaneous oral administration of soy protein to sensitize the dogs would have helped create a more physiologic model.

In sensitized dogs, a 50% reduction in the dermal inflammatory response was observed after oral administration of the hydrolyzed soy protein, compared with the response after oral administration of the native soy protein. Analysis of this observation suggests that contrary to the response after oral ingestion and although soy hydrolysate is less immunogenic, it still can induce a cutaneous reaction after ID injection.

Oral challenge testing revealed that sensitized dogs responded to native but not hydrolyzed soy protein. The fact that the study was a double-blinded controlled trial, together with the rapid appearance of signs of gastrointestinal tract reactions and pruritus after ingestion of soy protein, make this experimental method a useful tool to screen for oral immunogenicity of a hydrolysate. The clinical signs observed were those typically associated with adverse food reactions in dogs. Only 3 of the 6 sensitized dogs (the 3 with the highest response) had clinical signs. A positive correlation between serum IgE concentration and clinical signs was observed in all sensitized dogs. The major clinical response to oral administration of soy protein was evident in the dog with the highest IgE concentrations.

A similar oral challenge test was performed in the same 8 dogs (6 sensitized and 2 control dogs) when they were 12 months old (data not shown). At that time, none of the dogs had clinical signs after oral ingestion of native or hydrolysate soy protein. Three of the 6 sensitized dogs had clinical signs after oral administration of native soy protein when they were 2 years old. This was similar to results of a study[13] in which 2.5- and 3.5-year-old dogs that were allergic to peanuts did not react to initial challenge exposure to allergens. However, investigators in another study[15] described clinical signs in 15- to 18-month-old dogs after challenge exposure to milk; however, dogs in that study were part of a colony of hypersensitive dogs.

Even in the most reactive dog (highest IgE concentrations, highest response to intradermal testing, and the most gastrointestinal tract signs after oral challenge exposure to native soy protein), hydrolyzed soy protein did not induce clinical signs after oral ingestion. This observation agrees with that in a study[7] in which dogs with corn and soy allergies did not react to a diet containing soy hydrolysate and cornstarch. Apart from its low molecular weight, the extremely high digestibility of soy hydrolysate probably explains in part the reason that the fractions responded to by the skin are no longer responded to by the gastrointestinal tract. Indeed, dietary proteins properly digested prior to contact with the gastrointestinal mucosa will not activate the immune system.[9,11] Results of those studies[9,11] as well as results of a multicentric field study[10] support the benefits of a soy-based hydrolyzed diet for use in the diagnosis of adverse reactions to foods in dogs and management of affected animals.

The IgE concentrations did not correlate with the skin response associated with the native soy protein. Similarly, investigators in another study[7] observed that serum concentrations of soy- and corn-specific IgE and results of intradermal tests could not be used to predict clinical response in dogs after ingestion of those allergens. This suggests that oral challenge exposure is more predictive when evaluating the immunogenicity of soy protein, compared with the predictive value for intradermal testing. The current method of the use of dogs with allergies to soy is a helpful tool for evaluation of hydrolyzed soy protein and to assess the immunogenicity of soy protein from various sources.

In the study reported here, naïve Beagle pups were sensitized against soy protein and developed high serum concentrations of soy-specific IgE, had positive reactions during intradermal tests, and developed clinical signs after oral ingestion of native soy protein. When challenge exposed to hydrolyzed soy protein, sensitized dogs had reduced but definitive cutaneous responses as well as no clinical response after oral ingestion, even at high doses. Analysis of these results

suggests that soy hydrolysate may be a useful protein source for the management of dogs with soy allergies.

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Correction: Quantitative assessment of velocities of the annulus of the left atrioventricular valve and left ventricular free wall in healthy cats by use of two-dimensional color tissue Doppler imaging

In the report, "**Quantitative assessment of velocities of the annulus of the left atrioventricular valve and left ventricular free wall in healthy cats by use of two-dimensional color tissue Doppler imaging**" (*AJVR*, February 2006, pp 250–258) Jean-Louis Pouchelon, DVM, PhD, was incorrectly deleted from the list of authors in the byline.