The role of soybean meal hypersensitivity in postweaning lag and diarrhea in piglets

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Summary: *Many studies have been conducted to explain the postweaning lag period often described in pigs weaned onto a nursery diet that contains soybean meal as a protein source. Most researchers have concluded that some type of aberrant immune response to soy proteins plays a major role in this postweaning lag. This paper characterizes and describes the pathogenesis involved with the response to soy proteins in weaned piglets and recommends some practical ways to manage the problem.*

The gastrointestinal tract is continually exposed to antigenic stimuli, including nonpathogenic organisms, potential pathogens, and new dietary antigens. Although researchers have been aware of the allergenicity of soybean proteins and other food antigens in humans since the 1930s,[1] it is only recently that we have become aware of their role in animals.[2]

Animal species vary in their allergic sensitivity to soy proteins. Soy proteins have only weak sensitizing properties in guinea pigs and humans.[3] Preruminant calves are very sensitive to soybean meal proteins and are apparently unable to develop oral tolerance.[3,4,5] Weaned pigs exhibit a transient local hypersensitivity after they are exposed to soy proteins, but develop oral tolerance within 7–10 days.[5,6] The hypersensitivity response observed in pigs can be reproduced using the purified soybean proteins, glycinin and B-conglycinin.[7] Glycinin and B-conglycinin are considered to be the primary antigenic proteins responsible for soybean-meal hypersensitivity in weaned pigs.

Researchers do not agree on how to classify the immunological disease mechanisms associated with transient hypersensitivity in pigs. Many researchers believe the mechanism for soybean-meal hypersensitivity in pigs is a result of cell-mediated immunity (CMI).[6,8,9,10] The following findings in sensitized pigs support a cell-mediated mechanism:

- Stokes, et al., observed an increased number of intraepithelial lymphocytes (IELs) in the small intestine;[6]
- soy protein skin-test responses were histologically compatible with a delayed-type hypersensitivity reaction;[8]
- Miller, et al., observed lesions that were identical to those seen in mice during CMI reactions;[10] and
- Miller, et al., postulated that to produce a hypersensitivity, pigs must first be sensitized or "primed" by being exposed to the dietary antigen.[9]

The terms "delayed-type hypersensitivity" and "delayed transient hypersensitivity" often occur in the literature and are confusing because they describe the same reaction. For example, one study described the pig immune response to dietary soy antigens as a delayed transient hypersensitivity with no cell-mediated immune component.[7] A delayed hypersensitivity could imply a Type IV cell-mediated immunological disease (Table 1).

Some studies do not support a cell-mediated component. After pigs are orally exposed to soybean proteins, researchers consistently detect an increase in IgG antibodies, particularly to IgG_1. In preruminant calf studies, the hypersensitivity lesions were attributed to IgG_1 precipitating as an immune complex with soy antigen and the fixation of complement in the intestine.[3] Stimulating intraepithelial lymphocytes with mitogens (PHA and PWM) did not cause IELs to proliferate due to diet composition in a soybean-meal hypersensitivity trial.[7] Skin-fold thickness tests using mitogen PHA also demonstrated no difference between pigs exposed to soy proteins and those not exposed.[12] Other research has shown that "priming" is not necessary to elicit a transient hypersensitivity reaction in pigs.[13] In addition, the increased number of IELs observed following soy protein exposure in pigs may not support the theory of a cell-mediated mechanism for hypersensitivity. Over 80% of the IELs are T8 (CD8+) cells which have suppressor-cell functions and are probably responsible for the development of oral tolerance.[14] Most recently, the hypersensitivity response to soybean meal proteins in piglets has been classified as a Type III hypersensitivity.[15] Thus, the transient hypersensitivity and poor performance would be attributed to IgG_1 and soy protein precipitating as an immune complex in the intestine with fixation of complement.

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Table 1

Classification of Immunological Diseases[11]

Type of hypersensitivity	Pathological immune mechanism	Mechanisms of tissue injury
Type I: Immediate hypersensitivity	IgE antibody	Mast cells and their mediators
Type II: Antibody mediated	IgM, IgG antibodies against tissues or cell surface antigen	1. Complement activation 2. Recruitment and activation of leukocytes 3. Abnormalities in receptor functions
Type III: Immune complex mediated	Immune complexes of circulating antigens and IgM or IgG	1. Complement activation 2. Recruitment and activation of leukocytes
Type IV: T cell mediated	1. Delayed type hypersensitivity 2. T cell-mediated cytolysis	1. Activated macrophages, cytokines 2. Direct target cell lysis

Mechanism of immune response

The majority of dietary protein is digested into small particles that cannot stimulate an immune response. A small portion of these antigens are absorbed unaltered (<0.002%) and can be detected in circulating blood.[6] IgG titers specific for soybean proteins can be detected in pigs exposed to soybean meal.[2,7,8,15] The rise in soy-specific antibodies is correlated with a decline in circulating soy proteins.[8] Using I^{125}-labeled-soy, it has been shown that the decline in circulating soy antigens is a result of decreased absorption of the antigen rather than increased clearance.[2,8] This decreased absorption is accomplished by the immune system and is termed oral tolerance. The exact mechanisms involved with the establishment of oral tolerance are still unknown. It has been speculated that IgA continues to be secreted, binds the antigen to the intestinal mucosa, prevents further absorption, and allows breakdown from digestive enzyme activity.[2,6] Intraepithelial lymphocytes may play a primary role in the development of tolerance due to their suppressor cell activities.[14]

Pathogenesis

Pigs go through a transient period of hypersensitivity to soy proteins prior to establishing oral tolerance. The hypersensitivity response occurs within 3–4 days after adequate exposure to soy proteins and recovery occurs after 7–10 days.[6] During this period of hypersensitivity, pigs experience decreased growth performance and are more susceptible to enteric diseases.[9,10,13] After they develop oral tolerance, their growth performance will return to normal and they may demonstrate some compensatory gain.[7] Histologically, the intestinal morphology appears normal at 56 days post-exposure.[8] Researchers have speculated that the damage to the intestine is due to formation of complexes between systemic IgG_1 antibodies and residual soybean meal antigens plus complement activation.[15] The majority of the physiological and morphological changes observed in the intestine during a dietary hypersensitivity reaction can be associated with an accelerated turnover rate of enterocytes resulting in increased numbers of immature enterocytes lining the villi. These changes are listed below:

- villus atrophy;[7,9]
- elongated crypts;[7,9,10]
- increased mitotic rate of enterocytes;[6,10]

Cell-mediated immunity (CMI): An acquired immunity in which the role of T lymphocytes is predominant.

Intraepithelial lymphocytes (IELs): IELS are a subpopulation of T lymphocytes residing in the gut epithelium, usually found along the basement membrane.

Mitogens: A substance that induces cell division and proliferation.

Sensitivity: A state of abnormal responsiveness to an antigen. Failure to control these immunologic responses results in tissue damage and clinical disease.

Suppressor cell: Suppressor T cell function is to inhibit the activation of antigen-specific T and/or B lymphocytes.[20]

T8 (CD8+) cells: T lymphocytes possess detectable surface glycoproteins, which allow them to be divided into subpopulations with different functions. Two of these surface markers are CD4 and CD8. T4 lymphocytes have the CD4 marker and exhibit helper-cell activities. T8 lymphocytes have the CD8 marker and display suppressor cell functions as well as cytolytic activities.

Type IV cell-mediated disease: Disease resulting from tissue damage caused by a cell-mediated immune response to a specific antigen. The mechanism involves T lymphocyte (T helper cells) and their release of cytokines (soluble proteins or glycoproteins that mediate immune function) to activate macrophages.

- sloughing of mature enterocytes, increase in immature enterocytes;[6,10]
- decreased enzyme activity at brush border;[15,16]
- decreased absorption capability;[8,9,13,15]
- increased sensitivity to enterotoxins and secretory diarrhea;[8,15]
- decreased resistance to colonization of bacteria, especially hemolytic *Escherichia coli;* and[8,9]
- altered capacity to respond to nonrelated antigens.[6,8]

The majority of pigs in current swine production systems are first exposed to soybean meal at weaning or shortly thereafter. A transient hypersensitivity to soybean meal proteins at weaning can contribute to postweaning lag and predispose pigs to disease conditions such as *Rotavirus* and hemolytic *E. coli*.[9,10]

Hypersensitivity management

As stated earlier, pigs do not need to be primed to experience a transient hypersensitivity response to soybean meal after weaning. Basically, pigs will develop the hypersensitivity at the point in their life when they are exposed to adequate levels of antigenic soy proteins.[13] To minimize the negative impact of this response, it is important to choose the optimum time for piglets to acquire this hypersensitivity and develop oral tolerance. Most researchers agree that the ideal time to establish oral tolerance in piglets is before weaning. Studies have indicated that a total of 400–600 g (0.9–1.3 lb) of high-protein creep feed intake is necessary during lactation to induce oral tolerance in piglets while nursing the sow.[9,10,13] It is difficult to get pigs to consume this amount, particularly as the trend toward earlier weaning ages intensifies. Using oral or parental adjuvants may enhance the immune system's ability to develop tolerance with low prewean intakes.[8,17]

As pigs get older, they absorb less antigen, perhaps because their digestive function is improved and their mucosal immune system is more mature.[2] In one experiment, naive pigs no longer absorbed soy proteins when introduced into their diet at 6 months of age.[2] Because it is impractical to wait until 6 months of age to first expose pigs to soy proteins, and difficult to expose them to levels adequate to accomplish oral tolerance preweaning, most pigs will be exposed at some point between weaning and market. Feeding pigs a complex starter diet during the first week postweaning has been determined to be the most cost-effective time to induce a hypersensitivity reaction and develop tolerance.[18] Complex starter diets that use alternative protein sources such as plasma protein and milk products reduce the amount of soybean meal in the ration, which diminishes the clinical disease associated with transient hypersensitivity.[6]

Another way to manage soybean-meal hypersensitivity would be to decrease the antigenicity of the soy proteins by additional processing. Further processing of soybean meal decreases the hypersensitivity response, improves digestibility and growth performance.[15,19] Skin-fold thickness tests can be used as an indicator for the antigenicity of soybean meal products.[15] This simple test may be useful to determine the immunological quality of soybean meal products.

Conclusion

The role of soybean meal hypersensitivity should be considered in swine herds that have persistent problems postweaning. Clinical disease is typically a nonresponsive diarrhea postweaning and/or poor nursery growth performance. Managing this reaction can be economically significant, especially if the producer has finite finishing space and markets pigs based on age, not weight. Management strategies should be farm specific, depending primarily on age at weaning. The effects of medicated early weaning, modified-medicated early weaning, and segregated early weaning on degree of hypersensitivity compared to conventionally raised pigs is unknown.

Processing of soybean products significantly affects growth performance of nursery pigs. Further research is needed to develop a cost-effective soy product with low antigenicity and improved digestibility. Quality control of soybean products may need to include immunological criteria.

Implications

- Including less antigenic protein in starter diets will diminish the clinical disease associated with hypersensitivity. Use alternative protein sources, such as whey, skim milk, and/or plasma, to provide adequate protein in starter diets while using less than 20% soybean meal.
- Clinical disease may be diminished when you limit-feed starter diets that contain high concentrations of soybean meal. However, this practice will also decrease daily gain.
- Use a less antigenic form of soybean meal in starter diets. Further processing of the soybean meal into a more refined product will decrease the antigenicity of soy proteins. Currently, the cost for additional processing of soybean meal is prohibitive, but this may become cost-effective in the near future.
- You may be able to establish oral tolerance to soy protein during lactation by dosing piglets with soybean meal or purified antigenic soy proteins. You may need to dose the piglets several times over consecutive days.
- Weaning pigs at an earlier age may decrease the hypersensitivity response. Complement is not passively transferred to piglets in colostrum.[21] Pigs do not achieve adult levels of complement activity until day 14 of life. Conceivably, pigs weaned before they are 14 days old could be less sensitive to an immune response involving complement, as in soybean-meal hypersensitivity.

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