Dietary Plasma Protein Affects the Immune Response of Weaned Rats Challenged with S. aureus Superantigen B\textsuperscript{1,2}

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ABSTRACT The aim of this study was to determine the potential modulatory effects of diets supplemented with spray-dried animal plasma (SDAP) or immunoglobulin concentrates (IC) on the immune response of rats challenged with Staphylococcus aureus enterotoxin B (SEB). Lewis rats were fed diets containing 80 g of SDAP/kg diet, 22.7 g of IC/kg diet, or milk proteins (Control diet) from postnatal d 21 (weaning) for 14 d. On d 30 and 33, rats were given SEB (0.5 mg/kg body weight; i.p.). Organized gut-associated lymphoid tissue (GALT) populations, intestinal secretion, mucosal and serum immunoglobulin concentrations, and neutrophil infiltration were studied. On d 35, blood was collected under anesthesia and samples of intestinal mucosa, Peyer’s patches, mesenteric lymph nodes (MLN), and spleen were taken. SEB increased the water content of feces, which was prevented by diets containing either SDAP ($P < 0.002$) or IC ($P < 0.001$), indicating that plasma protein–supplemented diets can reverse the SEB-induced secretory response. In Peyer’s patches, the diet containing SDAP partially prevented the SEB-induced increase in T lymphocytes ($P < 0.1$) and reduced the percentage of activated T helper cells ($P < 0.05$). In MLN, activated T lymphocytes were increased by SEB but they were not affected by diet. No effects of SEB or dietary supplementation on mucosal IgA and serum IgA and IgG were observed. The effects of SDAP supplementation on the lymphocyte populations of GALT in rats challenged with SEB support the view that SDAP can modulate the immune response and suggest that plasma protein supplementation can prevent GALT from possible activation by luminal bacterial superantigens.

KEY WORDS: spray-dried plasma immunoglobulin concentrates intestinal inflammation rat Staphylococcus aureus enterotoxin B

Spray-dried animal plasma (SDAP) and serum proteins are complex mixtures of active proteins and other biologically important compounds that are used as additives in diets and supplements in farm animal production. SDAP promotes intestinal growth (1) and improves food intake and weight gain in postweaning pigs (2). These effects are more pronounced under conditions with a high number of pathogens than in environments with reduced potential pathogen exposure (3). This observation was confirmed by studies performed in animals challenged with pathogenic E. coli (4). This type of dietary supplement has been used as an alternative to antibiotics in the diet of young calves (5) and weanling pigs (6). Serum immunoglobulin concentrates (IC) improve viral gastroenteritis in children (7) and have been used in the treatment of diarrhea in AIDS patients infected with Cryptosporidium parvum (8). In both studies, significant reductions in stool frequency and weight loss were observed.

Mechanisms by which SDAP counteracts pathogen activity may include a reduction in pathogen adhesion. It was shown that several glycoproteins obtained from plasma can inhibit adhesion of E. coli to the small intestine (9). Moreover, immunoglobulins present in SDAP may bind to potential antigens in the lumen of the small intestine and prevent their attachment to mucosa and growth (10). Recent studies showed that SDAP reduces inflammatory cytokine expression in tissues exposed to lipopolysaccharide (LPS) (11) or E. coli (10). These results indicate that the mechanism of action of dietary SDAP and immunoglobulins on growth performance involves the immune system because the degree of immune cell activation may limit the availability of energy for growth (12) and may alter the structure and integrity of the intestinal mucosa (13). This hypothesis is consistent with the observa-
tion that SDAP can reduce tumor necrosis factor (TNF)-α expression in liver and spleen of farm animals exposed to thermal environment stress and challenged with LPS (14).

The objective of this study was to test the effects of SDAP and IC on cell populations of gut associated lymphoid tissue (GALT) and spleen, in rats challenged with enterotoxin B of *Staphylococcus aureus* (SEB). Staphylococcal exotoxins are potent activators of the immune system that can activate a high percentage of T cells by cross-linking major histocompatibility complex (MHC) class II molecules with a moiety on the variable portion of the β chain of the T-cell receptor (TCR) (15), hence called "superantigens." They cause a variety of diseases in animals and humans ranging from food poisoning to shock. Injection of SEB in mice and rats is often used as a model to study the immunological mechanisms of a superantigen-activated shock, in conjunction with other promoting agents (16) or by administration of a repeated dose of the same agent. We also investigated the effects of dietary SDAP and IC on neutrophil infiltration and mucosal water permeability, in rats challenged with SEB.

**MATERIALS AND METHODS**

*Animals and diets.* Male Wistar Lewis rats obtained from Harlan Ibérica were used throughout. Rats were kept under stable temperature and humidity conditions, with a 12-h light:dark cycle. At d 21 after birth, rats were weaned, distributed randomly into the various experimental groups and fed experimental diets until d 35. Groups studied were as follows: 1) healthy rats fed a control diet (Healthy); 2) rats fed a control diet and given SEB; 3) rats given SEB and fed a diet supplemented with spray-dried animal plasma (SEB-SDAP); and 4) rats given SEB and fed a diet supplemented with an immunoglobulin concentrate (SEB-IC). All protocols used in this study were approved by the ethical committees for animal experimentation of the Universitat de Barcelona and of the Regional Government (Departament d’Agricultura, Ramadera i Pesca, Generalitat de Catalunya). Rats were killed between 0900 and 1130 h by cervical dislocation under anesthesia.

Pelleted diets were formulated to meet NRC requirements (17) for laboratory animals (Table 1). SDAP is a feed ingredient obtained after separation of RBC by centrifugation of hygienically collected bovine blood from healthy animals (18). The IC was obtained by purification of the immunoglobulin fraction of bovine plasma (19). Both ingredients were spray-dried to obtain a stable powder product containing active immunoglobulins (175 g IgG/kg in SDAP and 617 g IgG/kg in IC). The maintenance of the native structure was checked by immunoelectrophoresis and Western blotting and the activity by an ELISA specifically recognizing *E. coli* (20). Diets supplemented with SDAP or IC were formulated to have a similar IgG concentration (14 g/kg of diet). Rats were monitored for daily food intake and body weight.

**Induction of intestinal inflammation.** Intestinal inflammation was induced by the i.p. administration of SEB (Toxin Technologies) dissolved in PBS. Preliminary experiments indicated that 2 doses of SEB administered with a 3-d interval resulted in higher myeloperoxidase (MPO) activity and water feces content than single doses of SEB. For this reason we used a protocol based on the administration of 2 SEB doses (0.5 mg SEB/kg body weight), the first on d 30 (d 9 after weaning) and the second on d 33. Healthy rats received PBS. Rats were killed on d 35 (i.e., after a 14-d dietary treatment).

**Water in feces.** At d 33, 34, and 35, spontaneously defecated stools were immediately collected and weighed. Feces were dried at 60°C for 3 d; the water content was measured and expressed as a percentage of the total wet weight.

**Determination of MPO activity.** MPO activity was measured as an indicator of neutrophil infiltration in mucosal samples from the jejunum. The jejunum was excised, flushed with PBS, and opened lengthwise following the mesentery line. The mucosa was scraped using glass slides, weighed, and immediately frozen at −80°C. For analysis, thawed samples were suspended in PBS, homogenized (Polytron, Kinematica), and centrifuged (1000 × g, 20 min); the supernatant was used for mucosal IgA determination. Mucosal MPO was determined following the method described by Fedorak et al. (21) using d-Orissidine (0.6 g/L, Sigma) and 0.001% (v/v) H2O2 (Sigma) solutions. Absorbance was measured every 15 s for 75 s at 460 nm in a UV-160A spectrometer (Shimadzu). One unit of MPO activity (U MPO) is defined as the amount of enzyme that degrades 1 μmol of H2O2/min at 25°C.

**Immunoglobulin determination.** Serum and mucosal IgA were measured by sandwich ELISA using mouse anti-rat IgA (ARA-1, Labgen; 1.25 mg/L) as capture antibody and rat IgA (IR22, Labgen) as standard. Serum IgG was also measured by ELISA, using mouse anti-rat IgG (STAR 71, Serotec; 0.25 mg/L) as capture antibody and purified rat IgG (Labgen) as standard. In both assays, horseradish peroxidase-conjugated mouse anti-rat IgG (RT-39 and RL-6, Sigma; 1:2000 dilution) was used as a secondary antibody. Color intensity was measured in a Microplate Reader (Multiscan, Labsystems).

**Preparation of lymphocytes samples.** Mesenteric nodes were excised and lymphocyte suspension was obtained by passage through stainless steel sieves in RPMI medium (Innogenetics) supplemented with 10% (v/v) heat-inactivated fetal calf serum (FCS; Innogenetics). Lymphocytes were then pelleted by centrifugation (600 × g, 10 min), resuspended in 2 mL of PBS containing 2% (v/v) FCS and 0.5 g/L sodium azide (PBS-FCS-Az). The lymphocyte pellet was then resuspended in 0.5 mL PBS-FCS-Az and cell counting and viability determination was done using acridine orange and ethidium bromide. In all cases, cell viability was >80%. The cell suspension was stored at 4°C until processing for immunostaining and flow cytometry.

To obtain spleen lymphocytes samples, the same protocol was followed; the only difference was an application of a NycoPrep gradient (Axis-Shield PoC AS) before the counting and viability determination.

To obtain lymphocyte suspension from Peyer’s patches (PP), the tissue was incubated in RPMI medium supplemented with 10% (v/v) FCS and 1 mmol/L of dithiothreitol (Sigma) for 5 min at 37°C. Lymphocyte suspension was obtained through stainless steel mesh and then centrifuged (600 × g, 10 min), resuspended in 44% (v/v) Percoll (Amersham Biosciences), and placed over 67.5% (v/v) Percoll. After centrifugation (600 × g, 30 min), the interface between the 44 and 67.5% layers was removed, and the cells were washed in PBS-FCS-Az and centrifuged (600 × g, 10 min).

**TABLE 1**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Control diet</th>
<th>SDAP diet</th>
<th>IC diet</th>
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<tr>
<td>Spray-dried animal plasma (SDAP)</td>
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<td>80</td>
<td>—</td>
</tr>
<tr>
<td>Ig fraction concentrate (IC)</td>
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<td>—</td>
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<td>Corn starch</td>
<td>149.3</td>
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<td>187.1</td>
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<td>Dried skim milk</td>
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<td>337.2</td>
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<td>Soybean oil</td>
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<tr>
<td>Cellulose</td>
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<td>50</td>
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<tr>
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<td>AIN-93 GM2</td>
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<td>DL-methionine</td>
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<td>3.2</td>
<td>2.7</td>
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<td>Choline bitartrate</td>
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<table>
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<tr>
<th>Nutrient composition</th>
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<td>Crude protein</td>
<td>182.6</td>
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<tr>
<td>Fat</td>
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<tr>
<td>Fiber</td>
<td>1.6</td>
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<tr>
<td>Metabolizable energy, kJ/g</td>
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</tbody>
</table>

1. APC Incorporated, Ankeny, IA.
2. Dyets Incorporated, Bethlehem, PA.
**RESULTS**

**Food intake and body weight.** Food intake, which was monitored from weaning (d 21) up to the end of the experimental period (d 35), did not differ among the groups (Fig. 1A). The estimated intake of dietary active IgG during the 14-d experimental period was 1.8 g IgG/rat. The mean body weight of rats at weaning was 45 g and the growth rate was similar in all groups, with no effect of SEB or dietary supplementation (Fig. 1B).

**Water content in feces.** At d 33 (i.e., just before the second SEB dose) there were no differences in the water content in feces between groups (Fig. 2). However, at d 34, there was an increase in the SEB group with respect to Healthy rats (P < 0.05). This increase was neutralized by dietary supplements in both the SEB-SDAP (P < 0.002) and SEB-IC (P < 0.001) groups. At d 35, the water content of feces from rats fed the diet containing SDAP was still significantly lower than the SEB group (P < 0.05).

**MPO activity.** Groups given SEB had a mucosal MPO activity (3.0 ± 0.41 UMPO/g mucosa) that was significantly higher than in Healthy rats (2.0 ± 0.13 UMPO/g mucosa; P < 0.05). Enzymatic activity of MPO in the groups SEB-SDAP (3.06 ± 0.37 UMPO/g mucosa) and SEB-IC (2.88 ± 0.35 UMPO/g mucosa) did not differ from that observed in the SEB group.

**Blood variables.** Hematological values were not modified by SEB treatment or dietary supplementation (data not shown). In Healthy rats, mucosal IgA (17.9 ± 1.15 μg secreted IgA/g), serum IgA (12.8 ± 0.85 mg/L), and serum IgG (975 ± 79 mg IgG/L) were not altered by either SEB treatment or dietary supplementation (data not shown).

**Effects of SEB and diets on lymphocyte populations.** In Peyer’s patches (Fig. 3), the SEB group had a higher percentage of T lymphocytes (P < 0.05) and a significantly lower proportion of B lymphocytes compared with Healthy rats (P < 0.05). SDAP and IC supplementation did not significantly modify the percentage of T and B cells in the SEB group. CD4⁺ T lymphocytes (T helper cells) were 12% of total lymphocytes, and SEB administration did not modify this percentage. For the supplemented groups, the percentage of this population was significantly increased in the group fed the IC-containing diet (P < 0.05), whereas there were no effects in rats fed SDAP. SEB induced a 15% increase (P = 0.093) in CD8⁺ lymphocytes (i.e., the suppressor/cytotoxic T population) compared with the Healthy group. No effects of diets were observed in the CD8⁻ population.

The activated T lymphocyte percentage in Peyer’s patches was significantly increased in the SEB group compared with Healthy rats (Fig. 3). In groups fed SDAP or IC supplements, no differences in activated T lymphocytes were observed with respect to the SEB group. SEB administration increased activated CD4⁺ cells from 3 to 5.4% (P < 0.01), and this increase was prevented by the SDAP-supplemented diet (3.4%; P < 0.05). The IC supplement also tended to prevent (P = 0.080) CD4⁺ activation (3.5%). Activated cells expressing the CD8⁺ phenotype did not differ between experimental groups.

In Peyer’s patches, the percentage of γδ-T lymphocytes increased after SEB treatment (P < 0.05). Although diets supplemented with SDAP or IC did not modify values obtained in the SEB group, there was a reduction in this population, with a pattern similar to that observed in the populations of total activated and CD4⁺ activated T cells (Fig. 3B). The NK cell population also tended to increase after SEB.

**Lymphocyte labeling by immunofluorescence.** Lymphocyte subsets were determined after double staining with a panel of anti-rat monoclonal antibodies and analyzed by flow cytometry. The phenotype of lymphocyte subsets were stained with anti-CD45RA (OX33 unconjugated, Pharmingen) to label B lymphocytes, anti-CD3 [G4-18, fluorescein isothiocyanate (FITC)-conjugated, Pharmingen] to stain T lymphocytes, anti-CD4 (W3/25, FITC-conjugated, Labgen) to detect T helper lymphocytes, anti-CD8 (OX-8, FITC-conjugated, Labgen) to label T suppressor/cytotoxic, anti-TCRαβ (RT3, unconjugated, Pharmingen) and anti-TCRγδ [V65, phycoerythrin (PE)-conjugated, Pharmingen] to recognize the cells expressing the corresponding TCR, anti-CD25 (NDS61, unconjugated, Labgen) to stain activated T lymphocytes and anti-NK-PIA (10/78, unconjugated, Pharmingen) to detect natural killer (NK) cells.

Cells (3 × 10⁵) were incubated with primary nonlabeled mouse monoclonal antibodies for 20 min at 4°C and subsequently washed in PBS-FCS-Az. Cells were incubated for 20 min with PE-conjugated goat anti-mouse IgG antibody (Sigma) diluted in PBS-FCS-Az containing 2% (v/v) rat serum to avoid cross-reactions. After a second wash, cells were incubated with normal mouse immunoglobulins (15 min at 4°C) and then labeled with FITC-conjugated antibodies (20 min at 4°C). Finally, cells were washed in PBS, fixed with 10 g/L paraformaldehyde, and stored at 4°C in the dark until analysis. For each rat, a negative control staining was included (human CD7). All antibodies were used at saturating concentration. Samples were counted in a flow cytometer (Epics Elite, Coulter).

**Blood determinations.** Total red and white blood cell counts, hematocrit, hemoglobin, and leukocyte differential counts were determined automatically by means of a Coulter Counter JT hemocytometer.

**Statistical analyses.** Means of replicate experiments were compared. Results are given as means ± SEM, n = 7–10. To analyze the effect of the enterotoxin administration, SEB rats were compared with the Healthy rats by an ANOVA using SPSS-10.0 software (SPSS). To study the effect of dietary supplementation on the intestinal inflammation model, rats fed the supplemented diets (SEB-SDAP, SEB-IC) were compared with rats fed the unsupplemented diet (SEB) by another ANOVA followed by Scheffe’s post-hoc test. Differences were considered significant at P < 0.05.
treatment (3.44 vs. 2.68% in Healthy rats; \( P = 0.094 \)), and no effect of diets was observed.

In the MLN, SEB treatment or the SDAP- and IC-containing diets did not modify the proportion of main lymphocyte populations. Percentages of T and B lymphocytes from spleen were not affected by SEB treatment or by the experimental diets (Table 2). Spleen CD4\(^+\) and CD8\(^+\) cells were not modified by SEB or by diets. The proportion of activated

T lymphocytes in MLN was increased by SEB treatment (2.0 ± 0.25% compared with 1.4 ± 0.17% in Healthy rats; \( P < 0.05 \)) but no effect of the experimental diets was observed (data not shown).

**DISCUSSION**

Few studies exist on the response of T cells of the GALT upon exposure to staphylococcal enterotoxin in the rat. The model employed in this study, based on the administration of 2 consecutive i.p. SEB doses, aimed to induce a mild inflammatory state with few repercussions on animal welfare, to avoid interference with the normal food intake pattern. The i.p. route is widely used in models of intestinal inflammation (15,22) because the oral route has the disadvantage that the amount of SEB reaching the mucosa is variable because it can be hydrolyzed by enteric enzymes, thus requiring coadministration of trypsin inhibitors (23). We chose rats at the weaning period because the mucosal immune system is still immature and therefore more susceptible to infection. In our model, food intake and growth rates were unaffected, indicating that basic intestinal and metabolic functions were not impaired. This is remarkable because the period chosen is a time at which rats (and mammals in general) move from liquid to solid food, thus becoming more susceptible to dietary and environmental aggressions (24).

In an intestinal inflammatory state there is mucosal neutrophil infiltration and hence increase mucosal MPO activity. Franco-Penteado et al. (25) observed an increase in MPO activity 4 h after subplantar injection of a single dose of SEB but this effect disappeared after 2 d. However, McKay et al. (26) did not find any increase in MPO activity 4 h or 2 d after i.p. administration of SEB in mouse jejunum. In our study, mucosal MPO was increased 2 d after the second SEB dose, indicating that the effects of the superantigen on neutrophil infiltration are long lasting. The increase in MPO activity was not prevented by the SDAP- or IC-supplemented diets.

Permeability of the intestinal epithelium is regulated by several stimuli, and enhanced paracellular permeability contributes to secretory diarrhea in humans and farm animals (27). Toxins such as SEB stimulate secretion of interferon (IFN)-\( \gamma \) and TNF-\( \alpha \) from lymphocytes; these cytokines disassemble tight-junction protein complexes and enhance paracellular permeability of microvascular endothelial cells (28). In the intestine, both effects eventually lead to alteration of the mucosal barrier and induction of intestinal secretion and diarrhea. TNF-\( \alpha \) can downregulate Na\(^+\)/K\(^+\)-ATPase in mice (29) and change Cl\(^-\) and K\(^+\) transport toward secretion in the human colon (30). Furthermore, IFN-\( \gamma \)-is involved in selective downregulation of intestinal Na\(^+\) absorption, in part by decreasing expression and activity of the apical membrane Na\(^+\) transporters NHE2 and NHE3 (31), which can also contribute to intestinal secretion.
Our study shows that SDAP and IC reduce an inflammatory marker such as diarrhea in SEB-treated rats, which may improve nutrient absorption and electrolyte homeostasis. Other studies performed with plasma supplements showed positive health effects; for example, oral supplementation of calves with bovine serum albumin can ameliorate C. parvum-induced diarrhea (32) and decrease the severity of disease in young calves exposed to coronavirus (33).

SEB administration or diets had no effect on hematological variables, which did not differ from reference values (34), or on serum immunoglobulins, which were similar to other rat strains (35,36). The observation that administration of SEB or dietary supplementation did not modify these systemic variables indicates that SEB actions are restricted mainly to the intestine. Interestingly, IgA levels in intestinal mucosa were not modified by SEB administration. This indicates that local stimulation of the immune system by SEB does not involve B-cell activation but T-cell-dependent enteropathy (15,23). The effect of SEB on T cells and T suppressor/cytotoxic populations in Peyer's patches of Healthy rats in our study is in agreement with studies performed in adult rats of several strains (37,38). In Peyer's patches, SEB increases the T lymphocyte population, supporting the view that SEB binds mainly to the TCR (15). When analyzing the activated lymphocytes within the 2 major subpopulations, CD4+ and CD8+, we observed that the main effect of SEB is circumscribed to the T helper cells, in agreement with results of McKay et al. (26) and Noel et al. (39). This increase in T helper activation was prevented by dietary supplementation with SDAP. The γδ T-lymphocyte values for the cytoxic cells in Peyer's patches from Healthy rats were in the range of values found for CBA/J mice (40). This population, together with the NK cells, increased when rats were treated with the double SEB dose, indicating that SEB also enhances cytoxic cell populations. This confirms previous observations in mice (41) and is consistent with observations in humans [γδ-T cells, (42); NK cells, (43)]. Dietary supplementation with SDAP brings the percentages of these cytoxic populations close to the values of Healthy rats. The different effects of SDAP and IC can be due to the different biological activity of their protein composition (SDAP contains all plasma components, whereas IC contains only the Ig fraction). Therefore, although immunoglobulins present in plasma may be the main agents responsible for SDAP activity, other functional proteins, such as transferrin, growth factors, and enzymes, may also contribute to the effects of SDAP.

The phenotypic study in MLN shows that treatment with SEB does not affect the percentages of the main lymphocyte populations. However, the number of activated T lymphocytes is increased, an effect that is not modified by experimental diets. The effect of SEB on activated MLN T helper cells was also reported after i.g. administration of the superantigen in mice (23). In the spleen, the cell populations were similar to those described for adult Lewis rats (44) and no effects of SEB were observed, supporting the view that SEB affects mainly the physiology of the intestinal epithelium (15). Because the systemic variables measured in the present study were not modified by SEB administration or diet supplementation, we conclude that the major effects of SEB and diets take place at the intestinal level, in agreement with previous observations (12,22).

The primary role of the immune response is the recognition, destruction, and elimination of antigens and pathogens. However, it is also clear that inappropriate immune reactions can result in tissue damage and pathology (26) that may lead to depression of growth. In this study, we showed that dietary SDAP and IC supplementation consistently reduced the percentage of several lymphocyte populations with specific functions in inflammatory states. The diet supplemented with SDAP prevented major activation of CD4+ cells produced by SEB, indicating that rats fed SDAP did not develop the same degree of activation of T helper cells. SDAP also prevented the increase in the γδ-T lymphocytes, which supports the hypothesis that a SDAP-containing diet can play a role in the modulation of the immune response by limiting the immune activation that would compromise the utilization of food energy (12). These systemic effects should be added to the well-known luminal effects of SDAP, preventing the activation of GALT by reducing the probability of bacterial agents and bacterial products reaching the intestinal mucosa (10).

The present study focused on the possible benefits of substituting conventional proteins with proteins prepared from animal plasma in preventing the symptoms of an experimental inflammation induced by the systemic administration of a superantigen. Our results show that SDAP (as well as IC, albeit to a lesser extent) protects GALT from possible activation provoked by S. aureus enterotoxin B. Extrapolation of the results obtained in the laboratory to the situation in farm animals is not straightforward because laboratory rats are not exposed to the same pathogen load that can affect farm animals. However, our results indicate a role for SDAP in limiting immune responses that could eventually compromise the utilization of energy from the diet.

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LITERATURE CITED


