MODULATION OF NUTRITIONAL STATUS BY THE IMMUNE RESPONSE

E.A. KOUTSOS and K.C. KLASING

Summary

An immune response to an infectious challenge changes the partitioning of nutrients away from productive processes such as growth toward the immune response and especially the production of acute phase proteins. We estimate that the immune system utilizes only about 1.2% of the lysine intake in a healthy growing broiler chick. During an infectious challenge, additional nutrients are needed to support the clonal proliferation of lymphocytes, formation of germinal centers, recruitment of new leukocytes from bone marrow, and the synthesis of acute phase proteins by the liver. These processes increase lysine needs for immunocompetence to 6.7% of intake. For some nutrients, like methionine and lysine, decreased growth completely compensates for increased needs for immunocompetence. The requirement for others, such as antioxidant nutrients, may be increased.

I. NUTRITION AND IMMUNOLOGY INTERACTIONS: AN OVERVIEW

The immune system is made up of a large number of cells and organs that interact to defend the body against non-self antigens. To be effective, the immune system must survey all possible sites of antigen entry (primarily mucosal tissue including the gut, nose, eyes, skin and lungs), be able to recognize and respond to an acute or chronic antigen exposure, and maintain memory of previous encounters.

The innate immune response is the first line of defense against an antigen and generally consists of antigen recognition, cell recruitment, phagocytosis and/or destruction of the antigen, and then presentation of antigen to other immune cells. In the course of the innate immune response, a cascade of cytokines (termed the pro-inflammatory cytokines) including interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) provide a communication network within the immune system as well as between immune cells and other cells of the body. These cytokines act locally and systemically to regulate immune responses, intermediary metabolism, and the endocrine system. The production, activity, and degradation of the pro-inflammatory cytokines are regulated by various factors including glucocorticoids, other cytokines, acute phase proteins, receptor antagonists and soluble receptors, as well as autocrine effects of the cytokines themselves. In addition, nutrition may affect the production of the pro-inflammatory cytokines as well as their regulators.

The acquired immune response consists of B and T lymphocytes that interact to defend the body against intracellular pathogens (primarily a cell mediated, cytotoxic T lymphocyte (CTL) mediated response), extracellular pathogens (primarily a humoral, B lymphocyte mediated response), and against tumor cells (accomplished by cell mediated and/or humoral responses, as well as by natural killer cells). These components of the immune system must respond to antigen that is presented by macrophages and other innate immune system cells, must be specific enough to respond to foreign antigen, but must not be auto-reactive. In addition, lymphocytes are responsible for maintaining memory of previous antigen exposure, and thus enabling a quicker, more effective response to a pathogen upon secondary exposure.

Department of Animal Science, University of California, Davis, CA, USA
II. IMPACT OF IMMUNE RESPONSES ON GROWTH AND NUTRITION: THE PROCESSES

Interestingly, reductions in production parameters associated with disease challenges are often a consequence of mounting an immune response rather than a specific effect of an invading pathogen on host tissue. For this reason, preventing exposure to pathogens through practices such as biosecurity programs, vaccination schedules, and feeding of antibiotics, probiotics or other compounds that can modulate gut microflora populations can prevent the onset of the immune response in the first place.

The first mechanism by which the immune system impacts nutrition is based upon the requirement for nutrients to maintain immune cell populations and to support proliferation and production of cytokines, antibodies, acute phase proteins etc. when a challenge occurs. The actual nutrient requirements to maintain and run the immune system have not been fully quantified, due to the diversity of cell types involved in various immune responses, the broad spectrum of possible immune responses, and the fact that immune cells are spread around the entire body, rather than being localized within a single organ. However, it has been demonstrated that the innate immune response is more nutritionally demanding than the acquired immune response. In fact, it is the production of acute phase proteins by the liver that comprises the majority of nutrient input into an immune response, while other immune processes such as antibody production are less costly (Klasing and Calvert, 2000).

The pro-inflammatory cytokine cascade directly modulates animal behavior. Lethargy, reduced social interactions, and anorexia result from the actions of IL-1 and TNF-α on the brain. These behavioral changes result in reduced feed intake and subsequent weight loss. Lethargy partially reduces the energy requirements for voluntary activity, thereby reducing the effects of anorexia on body catabolism.

An immune response can also alter intermediary metabolism. For example, the acute phase response to inflammation (APR) enhances skeletal muscle catabolism and hepatic protein synthesis, which is in direct contrast to the use of amino acids for skeletal muscle deposition during anabolic growth phases [see review by (Bistrian et al., 1992; Klasing, 1998a)]. This change in protein turnover within tissues reflects a need for substrates for production of the acute phase proteins, and presumably provides enhanced surveillance of cellular contents (including possible pathogens) by the immune system. In addition, the APR is associated with increased rates of glucose oxidation and gluconeogenesis, as well as increased hepatic lipid synthesis from fatty acids release by adipocytes (Beisel, 1977). Finally, antioxidants (particularly vitamin E) may be used to a greater extent during an immune response, to protect non-infected cells from the damaging effects of the reactive oxygen species by immune cells. Leukocytes release bursts of reactive oxygen species (ROS) when they encounter pathogens. ROS kill pathogens and cells infected by them; however, they also cause lipid peroxidation and DNA damage of non-infected cells that lack adequate antioxidant protection. For this reason, the requirement for antioxidant nutrients may be increased during an inflammatory response (Weibel et al., 1998; Yoshida et al., 1999).

Nutrient partitioning, or the localization of specific nutrients within tissues, may be altered during an immune response. As previously stated, amino acids are re-partitioned to the liver, where production of acute phase proteins occurs. Some acute phase proteins bind minerals, resulting in reduced plasma iron and zinc. Reductions in plasma mineral concentrations effectively "starves" pathogens of essential nutrients. While synthesis of metal-binding proteins is increased, synthesis of other proteins is reduced (negative acute phase proteins), also dramatically affecting plasma nutrient levels. For example, the production of retinol-binding protein is reduced during an immune response, resulting in
lowered plasma vitamin A during disease (Rosales et al., 1996). Concomitantly, triacylglycerol uptake by tissues other than the liver is reduced in response to APR [see review by (Grunfeld and Feingold, 1992)], resulting in increased plasma lipid levels. Additionally, hepatic fatty acid uptake is increased in response to the pro-inflammatory cytokines.

The immune response can directly impact nutritional status by modulation of nutrient absorption. In general, due to a reduction in food intake, nutrient absorption will be reduced overall. In addition, the absorption of specific nutrients is purposefully impaired. For example, dietary iron absorption is reduced, presumably to prevent pathogens from obtaining this limiting nutrient (Weinberg, 1974; Weinberg, 1999). Water absorption is significantly reduced by sepsis (Kanno et al., 1996), as is sodium, chloride and glucose absorption, and flux of these nutrients is often directed out of the body, as is the case with diarrhea.

An immune response has profound effects on the hormonal milieu. Pro-inflammatory cytokines decrease anabolic hormones such as growth hormone (GH) (Elsasser et al., 1997), insulin-like growth factor 1 (IGF-1) (Elsasser et al., 1995) and increase the release of catabolic hormones such as glucocorticoids [see review by (Elsasser, 2000)]. At the same time, a reduction in food intake also leads to reduced IGF-1 levels, thus promoting the catabolism of skeletal muscle. The APR is also associated with insulin resistance, as well as an increase in insulin and glucagon levels and subsequently, increased glucose oxidation (Wan et al., 1989). Hormonal modulation by the immune system provides an effective mechanism for changes in substrate partitioning.

If pathology occurs to a particular tissue during an immune response, metabolic and nutritional consequences may be severe. For example, intestinal pathogens may cause significant damage to the gut mucosa, thereby reducing nutrient absorption and enhancing blood loss (also directing nutrients away from the body). These pathogen-induced metabolic derangements must be added onto the purposeful alterations initiated by the immune system.

Once a bird has mounted an effective immune response and cleared a pathogen, levels of pro-inflammatory cytokines decline and food intake returns to normal. In fact, a period of compensatory growth typically ensues. The amino acid requirements to support compensatory growth are higher than normal. Presumably the requirements for other nutrients are increased as well. If higher levels of amino acids are not provided, the compensatory growth does not occur and the bird lags behind. Consequently, higher nutrient levels following the immune response are probably more important than during the immune response.

III. IMPACT OF IMMUNE RESPONSES ON GROWTH AND NUTRITION: THE RATES

We have recently attempted to estimate the quantitative needs of immune defenses in growing broiler chicks (Klasing, 1998b; Klasing and Calvert, 2000; Klasing and Leshchinsky, 1999). Lysine was used as the currency in this exercise - not because of any paramount importance of lysine, but because this amino acid is commonly used as a reference nutrient (e.g. ideal protein systems). In this exercise, we estimated the amount of lysine used to maintain an effective immune system in the absence of major infectious challenges and then added to the extra needs to support a robust innate and adaptive immune response triggered by a pathogen challenge.

The overall maintenance costs of owning an immune system can be put in perspective by examining the weight of immune tissues relative to body weight (Table 1). Nutritional costs of the immune system must also consider turnover rates of cells and macromolecules (Table 2). Nearly half of the lysine used for maintaining the immune system is for IgA secretion, especially along the mucosa. We estimate that the immune system utilizes only
about 1.2% of the lysine intake in a growing broiler chick and much of the rest is used for tissue accretion. However, maintaining the immune system accounts for about 10% of the maintenance component of the lysine requirement the chick.

When the immune system responds to an infectious challenge, additional costs include the clonal proliferation of lymphocytes, formation of germinal centers in lymphoid tissues for affinity maturation of immunoglobulin, the recruitment of new monocytes and heterophils from bone marrow, and the synthesis of effector molecules (e.g. immunoglobulin). Although the rate of synthesis of immunoglobulins (Ig) specific for a pathogen increase tremendously (Cohn and Langman, 1990), the total amount of Ig produced during most infections is not increased remarkably because most Ig are not directed toward the pathogen and the rate of their synthesis does not change. However, the production of acute phase proteins by the liver requires nutritionally relevant amounts of lysine. The high cost of an acute phase response likely explains why an infectious challenge causes changes in body condition and energy metabolism that are much greater than can be reconciled by summation of the substrates needed for leukocytes themselves. In the case of lysine, 6.7% of the intake is used to support the defensive responses, most of which is used for synthesis of acute phase proteins (Table 2). In total about 70% of the reduced performance that occurs during an infectious challenge can be attributed to decreased intake and the remaining 30% is due to inefficiencies (Klasing et al., 1987), including diversions to support the immune response.

Several experiments have examined whether higher concentrations of dietary nutrients ameliorate the impaired growth caused by an immune response. In the case of lysine, methionine, copper and zinc, high levels have little effect on growth rates (Klasing and Barnes, 1988; Klasing and Calvert, 2000; Koh et al., 1996). Increasing the energy density of the diet improves gain of broilers undergoing an acute phase response (Benson et al., 1995) but not turkeys (Piquer et al., 1995).

Table 1. Size of leukocyte pools1.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Concentration (10⁵/kg BW)</th>
<th>Mass (g/kg BW)</th>
<th>Lysine content² (μmol/kg BW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>15.2</td>
<td>2.43</td>
<td>170</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>6.93</td>
<td>1.39</td>
<td>97</td>
</tr>
<tr>
<td>NK cells</td>
<td>0.29</td>
<td>0.06</td>
<td>4</td>
</tr>
<tr>
<td>Macrophages/monocytes</td>
<td>1.1</td>
<td>0.28</td>
<td>19</td>
</tr>
<tr>
<td>Total of leukocytes</td>
<td>23.52</td>
<td>4.15</td>
<td>291</td>
</tr>
<tr>
<td>Total Ig³</td>
<td></td>
<td>1.28</td>
<td>736</td>
</tr>
<tr>
<td>Whole body</td>
<td></td>
<td>1000</td>
<td>70000</td>
</tr>
</tbody>
</table>

1From Klasing and Calvert, 2000.
2Assumes 70 μmol lysine per gram cells and 575 μmoles lysine/g Ig.
3Assuming that IgY and IgA concentrations in interstitial fluids are similar to that in blood plasma (BW = body weight; Ig = immunoglobulin).
Table 2. Daily rate of leukopoiesis, Ig synthesis, and growth in young chicks.  

<table>
<thead>
<tr>
<th>Process</th>
<th>Normal Production (mg/kg)</th>
<th>Normal Cost (µmol lys/kg)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>LPS challenged Production (mg/kg)</th>
<th>LPS challenged Cost (µmol lys/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopoiesis in all tissues</td>
<td>650</td>
<td>45.5</td>
<td>1300</td>
<td>90.9</td>
</tr>
<tr>
<td>Ig synthesis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>114</td>
<td>65.6</td>
<td>121</td>
<td>69.6</td>
</tr>
<tr>
<td>Acute-phase protein synthesis&lt;sup&gt;4&lt;/sup&gt;</td>
<td>~0</td>
<td>~0</td>
<td>710</td>
<td>386</td>
</tr>
<tr>
<td>Total for immunocompetence</td>
<td>764</td>
<td>111.1</td>
<td>2131</td>
<td>546.5</td>
</tr>
<tr>
<td>Body weight gain&lt;sup&gt;4&lt;/sup&gt;</td>
<td>85000</td>
<td>5950</td>
<td>72446</td>
<td>5212</td>
</tr>
<tr>
<td>Lysine intake</td>
<td>-</td>
<td>9520</td>
<td>-</td>
<td>8311</td>
</tr>
<tr>
<td>% of intake used for immune</td>
<td></td>
<td>1.17</td>
<td>-</td>
<td>6.71</td>
</tr>
<tr>
<td>processes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of intake used for growth</td>
<td></td>
<td>62.50</td>
<td></td>
<td>62.70</td>
</tr>
</tbody>
</table>

<sup>1</sup>From Klasing and Calvert, 2000.

<sup>2</sup>Data are on a kg body weight per day basis.

<sup>3</sup>Assuming the 25% increase in Ig requires 4 days to accomplish (as in a secondary exposure to an antigen).

<sup>4</sup>Data taken from 14 d broiler chicks.

IV. CONCLUSION

The first priority for animal production systems must be to reduce the incidence of disease challenges. Secondly, changes in diet formulation should be made during disease challenges to account for reduced food intake. Finally, after an immune response, dietary strategies must account for compensatory growth and for regeneration and healing of damaged tissue.

Nutrient requirements to maintain a capable immune system must account for maintenance of immune cell populations, their normal cellular functions and the memory of previous exposures. In addition, mounting an immune response may modify the use and/or supply of nutrients. These nutrients may be derived from dietary sources, but often are re-partitioned from productive processes such as growth and reproduction to the immune response. At the same time, voluntary food intake and activity are reduced in diseased animals, resulting in reduced nutrient uptake and subsequent weight loss.

When formulating diets for animals facing disease challenges, it is important to remember that food intake may be depressed. Therefore, if some nutrients are required at increased levels during disease (eg. antioxidant nutrients), the actual level of incorporation of these nutrients into the diet must be greater to overcome the reduction in dietary intake. For this reason, it may be necessary to formulate diets for pre-exposure, disease states, and recovery periods.

REFERENCES


