THE ROLE OF PROTEIN AND AMINO ACIDS IN IMMUNITY

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INTRODUCTION

The immune system manages the amount and location of pathogens within the body. Activation of the immune system occurs at the expense of growth. While it is important for the animal to resist disease, the decline in animal performance is the trade-off associated with immune system activation. Improvements in animal production and productivity can be achieved, at least in part, by balancing immune responsiveness with desired performance outcomes. Protein and amino acid nutrition is tightly interwoven into immunophysiology. Understanding these relationships will provide a better understanding of how protein and amino acid nutrition can be used to help provide nutritional support to the immune system.

IMPACT OF AN IMMUNE RESPONSE ON AMINO ACID METABOLISM AND REQUIREMENTS

Activation of an innate immune response results in skeletal muscle degradation and a negative nitrogen balance. Catabolism of skeletal muscle releases amino acids into the plasma and these substrates are available for use by tissues and cell types involved in host defense (Klasing et al., 1984, Klasing et al., 1984). Consequently, activation of the innate immune system results in the repartitioning of amino acids from growth toward immunity (Humphrey et al., 2004).

The shift in amino acid consumption from growth to immunity results in a shift in the amino acid composition of proteins being synthesized. The rates of amino acids incorporated into skeletal muscle proteins are reduced while the rates of amino acids incorporated into proteins involved in host defense, such as acute phase proteins, are increased. These proteins differ in their amino acid composition and this change in amino acid profile may also be reflected in the diet. Reeds (Reeds et al., 1994) first hypothesized that the high rates of skeletal muscle catabolism during periods of infection are due to the high demand for specific amino acids whose proportions are particularly high in acute phase proteins. By comparing amino acid profiles of several acute phase proteins to skeletal muscle, aromatic amino acids appear to be in greatest demand due to their low proportion in skeletal muscle and high proportion in acute phase proteins (Reeds et al., 1994). Consequently, skeletal muscle is catabolized to supply amino acids for acute phase protein synthesis in an amount sufficient to supply aromatic amino acids, specifically phenylalanine, while the surfeit levels of other amino acids liberated from skeletal muscle are excreted and contribute to the negative nitrogen balance of the animal (Reeds et al., 1994). Thus, catabolism of skeletal muscle is an important metabolic alteration during infection since this

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process provides amino acid substrate for the liver to synthesize acute phase proteins. Rather than implementing nutritional support to prevent skeletal muscle degradation, efforts may be best served by providing the composition of amino acids that are ideal for the synthesis of protective factors, such as acute phase proteins. As an example, recent studies by Faure et al (Faure et al., 2007) have shown in rats that threonine utilization for synthesis of acute phase proteins and intestinal mucins is increased during infection.

Altered amino acid metabolism encountered during infection influences the amino acid requirement of growing animals. Methionine and lysine requirements for gain and feed efficiency are decreased in growing chicks engaged in an innate immune response (Klasing et al., 1988). Presumably, decreased growth and protein accretion reduce the need for methionine and lysine as substrates for protein synthesis (Klasing et al., 1988). The total digestible lysine requirement is lower in chicks challenged with LPS, while the total digestible arginine requirement is unaffected (Webel et al., 1998, Webel et al., 1998). However, the efficiency at which lysine and arginine are used for protein accretion is similar in infected and non-infected chicks (Webel et al., 1998, Webel et al., 1998). The decline in food intake during an innate immune response does not cause a change in dietary lysine or threonine required to maximize protein accretion (Webel et al., 1998). Therefore, matching the dietary lysine, threonine, or arginine intake of infected chicks to that of healthy chicks would not be expected to improve lean body mass.

AMINO ACID NEEDS FOR IMMUNITY

Nutrition can regulate the type of immune response by a number of mechanisms (Klasing, 2007). Amino acids regulate immunity be serving as substrates for the development, maintenance and use of immune system. Consequently, the supply of amino acids at the appropriate amounts, times and ratios are important for immunity.

The immune system consists of numerous tissue and cell types that are responsible for the production of a vast array of effector molecules involved in pathogen killing and in the regulation of the immune response (Table 1). The specific amino acid requirements for these cells, tissues, molecules and processes have been based upon empirical growth trials, yet it is not known if the amino acid requirements for growth are indeed optimum for immunity. Consequently, the amino acid needs for the immune system is an outstanding question. Utilization of classical approaches for determining nutrient requirements may not be best suited for determination of amino acid needs for immunity. Based upon the diversity of immune cells, tissues, molecules and responses (Table 1), determining a dietary amino acid requirement that is optimum for all of these variables and their combinations is impractical since not all components of the immune system respond at all times in the same manner to all pathogens. Rather, more focused approaches that aim to determine optimum amino acid needs for specific cell types and specific responses to pathogens are needed.

Table 1. Nutrient consuming components and processes of the immune system.

Lymphoid tissue	Leukocytes	Molecules	Processes
Bursa	B cells: naïve, effector, memory	Mucus	Inflammation
Thymus	T cells: T helper (T_H), T cytotoxic (T_C), T_H/T_C naïve, T_H/T_C effector, T_H/T_C memory	Cytokines	Acute phase protein production
Lymph node	Natural killer cells	Antimicrobial peptides	Lymphocyte development
Spleen	Monocytes/ Macrophages	Antibody	Lymphocyte clonal proliferation
Mucosal associated lymphoid tissue	Dendritic cells	Reactive oxygen species	Synthesis of new leukocytes
Hardarian gland	Neutrophils	Acute phase proteins	Phagocytosis
Blood	Eosinophils	Reactive nitrogen species	Chemotaxis
Germinal Centers	Basophils	Antioxidants	Wound healing
	Thrombocytes	Complement	Mucosal barrier turnover
	M cells	Heat shock proteins	Allergy Autoimmunity

SUPPLYING AMINO ACIDS TO THE IMMUNE STYSTEM: PUSH VERSUS PULL

When considering diet modifications to help feed the immune system and optimize animal health, it is important to consider the concept of push versus pull in regards to amino acid partitioning to the immune system. A common approach aimed to increase activity of the immune system is to include more of a particular amino acid that is suspected to be in limited supply in the diet or during a particular physiological state. This "push" approach to feeding the immune system assumes that more is better and is fundamentally based upon the idea of tissue competition for amino acids, such as skeletal muscle versus immune tissue. The "push" approach to feeding the immune system assumes that providing more amino acids in the diet will increase their utilization by the immune system. However, simply increasing the supply of a particular amino acid does not necessary directly translate to increased utilization. For example, increased dietary arginine levels will result in increased growth, yet this does not translate into increased growth of lymphoid tissue (Kidd et al., 2001). These events are also regulated by signaling systems that act independent of the amino acid supply, per se. Consequently, the

"push" approach to feeding the immune system is based upon amino acid supply alone and does not consider the controls that couple amino acid supply with demand. In regards to feeding the immune system, it is important to understand how these cell types and tissues coordinate amino acid utilization.

The "pull" approach to feeding the immune system involves modulating the coordinated adaptations that direct nutrient partitioning toward immune function. These adaptations are complex and regulated by signals, often times cytokines, to help coordinate nutrient supply with nutrient demand across all tissues and within the animal (Humphrey et al., 2004). The coordinated adaptations of nutrient utilization throughout the body by signals from the immune system help to ensure that nutrient supply meets the nutritional demands associated with immune function.

Coordination of nutrient partitioning to the immune system is achieved in large part through the actions of cytokines. Leukocytes display many cytokine receptors, but other cell types have a much more limited expression pattern. This difference allows cytokines to act selectively upon cells of the immune system to increase their nutrient acquisition. Furthermore, the selective action of cytokines can affect nutrient acquisition by specific leukocyte populations. For example, activated T lymphocytes produce interleukin-2 (IL-2) that acts in an autocrine and paracrine manner to increase T lymphocyte proliferation. IL-2 also increases T lymphocyte glucose transporter-1 (GLUT-1) protein to provide energy for proliferation. During lymphocyte development, IL-3 also increases lymphocyte nutrient transporters for glucose, amino acids, lipids and metals (Edinger et al., 2002) and IL-7 maintains the metabolic activity of naïve T lymphocytes (Rathmell et al., 2001).

TAKE HOME MESSAGES

When formulating diets that are optimum for the immune system, it is important to consider the type of nutrients being offered to the immune system, i.e. supply, and to what specific aspect of the immune system that they are intended for, i.e. demand. Considering supply without demand can result in either no impact on immune function, or even decreased overall animal health, as evidenced by the severity of *E. coli* infection in iron supplemented newborn pigs (Kadis et al., 1984). Rather, nutritional approaches to enhance immune function should focus on supplying the nutrients at the appropriate times and in the appropriate amounts that complement the "pull" associated with increased nutrient partitioning for immune function.

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