

Nutritional Costs of an Immune Response

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Introduction:

It is well known that disease challenges reduce the production of meat, milk and eggs, reduce breeding success, and are economically very detrimental to producers. Interestingly, reduced productivity as a consequence of disease challenge is often due to the effects of mounting an immune response rather than the effects 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. Additionally, an understanding of the immune system and its interactions with the nutrition of an animal can allow for optimal diet formulation before, during and after a disease challenge. This type of strategy can help to maximize the immune response to invading pathogens, while minimizing the deleterious effects of an immune response on the host.

Immune system 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. There are two major components of the immune response that are responsible for achieving these goals: the innate and the acquired immune systems.

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 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, PIC) including interleukin 1 (IL-1), IL-6 and tumor necrosis factor- α (TNF- α) provide a communication network between immune cells and other cells of the body. These cytokines act locally and systemically to drive the innate immune response and to induce some facets of the acquired immune response. 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.

The acquired immune response generally occurs at a later time period than the innate immune response, and consists of B and T lymphocytes that interact to defend the body against intracellular pathogens (primarily a cell mediated, cytotoxic T lymphocyte (CTL) response), extracellular pathogens (primarily a 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.

Interactions between the immune system and nutrition:

There are a variety of ways in which the nutritional status of an animal interacts with its immune system and vice versa. An animal's nutritional status can directly impact immune function by a variety of mechanisms including direct effects of a nutrient on the development or function of the immune system, or through indirect effects of nutrients, such as regulation of hormonal milieu or gene expression (see review by 1). In a similar manner, an immune response can impact the nutritional status of an animal by several mechanisms. First, development and maintenance of the immune system requires nutrient input, which must be supplied by the diet. Second, an immune response may directly impact nutrition by modulating animal behavior, substrate supply and use, or nutrient partitioning. Third, the pathology associated with an immune response may directly impact the nutrition and metabolism of an animal. Finally, the immune response impacts nutrition by indirect mechanisms as well. For example, modulation of hormone profiles by cytokines can significantly impact growth and production.

Nutritional costs of maintaining an immune system:

The first mechanism by which the immune system impacts nutrition is based upon the nutrients required to maintain large immune cell populations and to support cellular 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 generally 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 (2). However, during the acute phase response, feed intake is reduced, so the plane of nutrition prior to disease challenge will be used to support the needs for acute phase protein production.

Effects of an immune response on behavior:

Mediators of the immune response, primarily the PIC cascade, directly modulate animal behavior. Lethargy, reduced social interactions, and anorexia result from the actions of IL-1 and TNF- α on the brain (3). These behavioral changes result in reduced feed intake and subsequent weight loss. In theory, lethargy can reduce the energy requirements for voluntary activity, thereby reducing the effects of anorexia on body catabolism. However, the net energy expenditure during disease typically exceeds the nutrient intake, and thus weight loss ensues.

Effects of an immune response on hormonal milieu

An immune response has profound effects on the hormonal milieu. PIC actions reduce the production of anabolic hormones such as growth hormone (GH, 4) and insulin-like growth factor 1 (IGF-1, 5), and increase the release of catabolic hormones such as glucocorticoids (see review by 6). At the same time, depressed food intake also leads to reduced IGF-1, thus promoting the catabolism of skeletal muscle (4). Inflammation is also associated with insulin resistance, as well as an increase in insulin and glucagons levels and subsequently, increased glucose oxidation (7). Hormonal modulation by the immune system provides an effective mechanism for changes in nutrient partitioning, which may provide substrates for the immune response and/or prevent pathogen acquisition of limiting nutrients.

Effects of an immune response on nutrient use and partitioning:

The effects of an immune response on nutrient use and partitioning can be quite dramatic, and examples of these changes have been described for amino acids, energy, lipids, minerals, and vitamins. Alterations in nutrient use and partitioning may be the result of reduced nutrient intake and/or nutrient absorption, changes in the production of binding and transporter proteins, or may be induced by the pathology of the immune response.

The effect of an immune response on protein metabolism has been well-documented; inflammation, and the PIC cascade 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 8). 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 proteins by the immune system.

The use of substrates for energy is also altered by an immune response. Inflammation is associated with increased use of glucose as an energy substrate, characterized by increased rates of glucose oxidation and gluconeogenesis. Concomitantly, the oxidation of fatty acids as a source of energy is reduced (9). Alterations in lipid metabolism are the result of PIC-induced increases in adipocyte fatty acid release, hepatic lipid synthesis (9), and hepatic triacylglycerol secretion (10) as well as reductions in lipoprotein lipase (LPL) activity. Reductions in LPL activity, induced by TNF- α , result in reduced triacylglycerol uptake by extra-hepatic tissues (see review by 11), and when combined with increased lipoprotein export from the liver, result in increased plasma lipid levels. Additionally, it has been demonstrated that immune responses are often associated with increased retained energy as lipid (12, 13), presumably as a result of altered glucocorticoid production.

Mineral partitioning is also affected by an immune response. For example, calcium metabolism is altered such that bone mineral density is reduced, while blood calcium levels are enhanced (see review by 14). The biological basis for this change has been hypothesized to be increased surveillance of bone tissue, although experimental evidence is currently lacking. Plasma iron levels are reduced during the acute phase response, in association with increased hepatic transferrin and/or lactoferrin production. This reduction serves to prevent pathogen acquisition of this limiting nutrient, while reductions in intestinal iron absorption facilitate pathogen deprivation (15, 16). Plasma zinc levels are also reduced by an immune challenge, as a result of increased liver metallothionein production (17). Increased hepatic zinc provides a co-factor source for many of the hepatic acute phase proteins.

The use and partitioning of vitamins is dramatically altered during an immune response. As previously mentioned, the deleterious effects of an

immune response often result in 'collateral damage' to the host. In particular, the production of reactive oxygen species (ROS) is enhanced during an immune response to kill and neutralize invading pathogens, but may cause lipid peroxidation and DNA damage to non-infected host cells. For this reason, antioxidants (particularly vitamin E, also vitamin C) are often 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, and the requirement for antioxidant nutrients may be increased during an inflammatory response (18, 19). Changes in vitamin A metabolism are also apparent during disease challenges. Retinol-binding protein (RBP), the vitamin A transport protein, is a negative acute phase protein, and as such, hepatic synthesis of this protein is dramatically reduced during an immune response (20, 21). The primary consequence of reduced RBP synthesis is that hepatic vitamin A cannot be transported to extra-hepatic tissues, and consequently plasma vitamin A levels are significantly reduced by disease. Additionally, it has been demonstrated that some tissues (e.g. lung) have reduced tissue retinol levels at an earlier time points during disease challenge than the time at which plasma retinol levels are reduced (22). These data suggest that at least in some tissues, retinol is being consumed at a greater rate in response to inflammation, although the exact function of vitamin A during inflammation is unclear. Finally, alterations in local vitamin D metabolism have been recently reported. *In vitro* studies have shown that synthesis of the active metabolite of vitamin D (1,25 dihydroxycholecalciferol, 1,25-D₃) is induced in endothelial cells by inflammatory cytokines, and promotes leukocyte adhesion to endothelial cells (23). Additionally, 1,25-D₃ has been shown to induce differentiation of monocytes and suppress cell-mediated immune responses (see review by 24). Therefore, alterations of 1,25-D₃ levels locally may affect the immune response, without modulating systemic calcium levels.

Finally, the partitioning of nutrients that are not considered essential is also altered by disease challenge. The most notable example of this occurs in birds, in which viral, bacterial and parasite challenges are associated with reductions in carotenoid-based pigmentation (25-28). These changes are often a result of reduced dietary absorption and increased losses through intestinal bleeding (eg. intestinal parasites such as coccidian, 27). Additionally, changes in carotenoid-based pigmentation are likely a by-product of altered lipid metabolism; since many carotenoids are transported with lipoprotein particles, changes in lipoprotein synthesis and uptake may play a significant role in carotenoid partitioning during an immune response. Finally, as is the case with vitamin E, carotenoids may play a functional role in immune responses, given their antioxidant potential and other immunomodulatory functions, and thus may be metabolized at a greater rate during an immune response.

Conclusions:

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 (e.g. Vitamin E). 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 diet sources, but often are re-partitioned from productive processes such as growth and reproduction to the immune system and its components. At the same time, voluntary food intake and activity are reduced in diseased animals, resulting in reduced nutrient uptake and subsequent weight loss. 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.

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