FEEDING THE IMMUNE SYSTEM: ENERGY AND PROTEIN NEEDS FOR IMMUNOCOMPETENCE

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The Immune System: An Overview

The immune system utilizes a combination of constitutive and adaptive mechanisms that interact with one another to protect the host from microorganisms and infectious disease. Constitutive defenses of the innate immune system consist of effector cells, such as monocytes/macrophages and neutrophils, along with mucosal and epithelial barriers, secretions and plasma acute phase proteins. The innate immune system is capable of recognizing foreign invaders, i.e. non-self, and functions as the first line of defense against these potential disease causing microorganisms, or pathogens. The adaptive arm of the immune system is capable of selectively recognizing and eliminating foreign microorganisms or molecules. These functions are mediated by immunoglobulin secretion by B lymphocytes and various cellular functions mediated by T lymphocytes, collectively referred to as humoral and cell mediated immunity, respectively. Both humoral and cell mediated immunity have tremendous diversity in their recognition molecules and their response to non-self results in immunological memory. Consequently, animal health and disease resistance is achieved through the collective actions of innate, humoral and cell mediated immunity.

Nutritional status and nutrient availability have a major influence on the development, maintenance and function of innate, humoral and cell mediated immunity.[13] An alteration in resource availability, such as energy and protein/amino acids, triggers metabolic adaptation and reallocation of existing nutrient stores to support different life-traits. Interestingly, the immune system is varied in its response to nutritional status and nutrient availability, particularly as it relates to energy and protein/amino acid status. Consequently, the interactions between nutrition and immunity have important implications on animal health and well-being.

Interactions between Energy Intake and Immunocompetence

Energy Requirements for Immunity

Energetically expensive physiological traits, such as reproduction, are often linked with periods of high-energy availability and in many animals the cue for energy availability is linked to day length. Consequently, the breeding season for many animals is linked to increasing day length since this also coincides with increased energy availability to support the growth of reproductive tissues and offspring. The energy requirements are not as timely for the immune system, however, since the immune system must be poised at all times to fend off invading microorganisms, regardless of energy availability, to ensure survival. Consequently, utilization of the immune system requires energy repartitioning toward host defense and the amount of energy utilized by the immune system depends in large part upon the type of immune response elicited, i.e. innate or adaptive immune response.

The innate immune response has the greatest potential for altering energy requirements due to its ability to modulate the neuroendocrine system. Activation of the innate immune system results in the secretion of proinflammatory cytokines that communicate to the hypothalamus to increase body temperature and induce fever.[14] The increase in heat production associated with fever has been proposed as a major contributor to changes in energy requirements during periods of infection.[11] Activation of the innate immune system in chickens increases liver and spleen size and heat production, indicating an altered energy requirement during this period of infection.[4,12] Indeed, animals fed diets in excess of their metabolizable energy (ME) requirement by carbohydrate addition did not decrease growth,[4] suggesting that repeated activation of the innate immune system may result in a higher ME requirement for growth in chickens.

The utilization of energy resources by the innate immune system may come at a cost to other physiological systems. For example, feeding livestock subtherapeutic levels of antibiotics or rearing them in germ-free conditions results in increased growth due to decreased activation of the innate immune system.[31] In lizards, egg laying, or reproductive output, is decreased in response to activation of the innate immune system.[36] In house sparrows, blunted innate immune responses are associated with invasion success, presumably due to less energy use being partitioned toward immunity and more towards invasive efforts and behaviors.[20] Since the innate immune system is the first to respond to pathogen, changes in energy requirements associated with the innate immune system are likely to occur during the early stages of infection and are typically transient due to the short duration of innate immune responses. Additionally, since the innate immune system does not have memory toward specific pathogens, energetic costs associated with activation are similar upon repeated pathogen exposure.[10] The inability of the innate immune system to increase efficiency of energy use upon repeat pathogen exposure is a major difference between energy use by the innate and adaptive immune systems.

Unlike an innate immune response, activation of an adaptive immune response has little to any cross-talk with other physiological systems, such as that between innate immunity and the neuroendocrine system. Activation of antigen specific lymphocytes results in their proliferation and secretion of immunoglobulin (B cells) or regulatory factors (T cells). Consequently, energetic costs are associated primarily with cell proliferation and the synthesis of effector and regulatory molecules. This is in contrast to the innate immune system, where activation results in a systemic response that results in alterations in multiple physiological systems.[16] Nevertheless, the adaptive immune system has often been considered to be energy demanding. The energetic cost of mounting a primary adaptive immune response has been reported to be 1.6-2.6 kJ in blue tits[34] and 23.4 kJ in mice.[6] In chickens, mounting a primary response increased heat production by 6.5%.[32] The energetic cost of a cell mediated immune response in house sparrows has been reported to be 4.2 kJ per day.[23] Since the adaptive immune system requires several days to develop, the energetic cost summed over this time period approach or even equal energetic costs of other physiological activities,[23] indicating that primary adaptive immune responses may be a significant competitor for energy resources.

The ability of the adaptive immune system to develop immunological memory has important implications on energy utilization and needs. Immunological memory results in greater numbers of antigen-specific cells capable of responding to antigen upon repeat exposure, so secondary adaptive responses are shorter in duration and much more robust. Consequently, the energy needs for secondary adaptive immune responses are anticipated to be lower than primary adaptive immune responses due to the decreased need for synthesis of effector cells.[9]

Impact of Energy Intake on Immunity

Intake of excess calories results in storage of feed energy as adipose and this endocrine tissue produces regulatory molecules, or adipokines, that not only regulate food intake but also immunity. Consequently, alterations in fat stores may affect immunity indirectly by changes in endocrine signaling within the immune system. Leptin is synthesized in response to body fat mass and plays an important role in regulating metabolism. Leptin also is a regulator of innate and adaptive immunity and promotes more pro-inflammatory immune responses.[19] Other adipocytokines include tumor necrosis factor-α and interleukin-6 that also promote inflammatory responses. Therefore, adipose tissue is capable of biasing the immune system through the release of endocrine factors that regulate immune cell function.

Reduced food intake, or decreased energy intake, results in the release of glucocorticoids that are immunosuppressive. Elevated corticosterone in response to decreased energy intake results in deletion of developing B and T lymphocytes and lymphopenia.[8] Surprisingly, production of cells of the innate immune system increased when energy intake was restricted,[18] indicating that reductions in energy intake may result in the developmental reprogramming of the immune system.

Leukocyte Energy Substrates

Energy metabolism is of particular importance to lymphocytes since their development and activation involve rapid proliferation. Cells of the innate immune system also have an energy demand, though this is assumed to be not of the same magnitude as lymphocytes. Leukocytes primarily utilize glucose and glutamine as an energy source.[3] Glucose is the fuel of choice for lymphocytes, and in mammals glucose is actually an essential nutrient for lymphocytes.[9] Glucose is also important for generating reducing equivalents through the pentose phosphate pathway. These reducing equivalents are essential for producing killing compounds involved in the macrophage respiratory burst.[27] Second to glucose, glutamine is also a major energy substrate for leukocytes. Like glucose, glutamine metabolism can also generate reducing equivalents necessary for the production of reactive oxygen species.[26] Glutamine conversion to glutamate may also aid in the transport of amino acids since glutamate is a substrate for many amino acid transport exchange systems.[1]

Interactions between Nitrogen and Amino Acid Nutrition on Immunocompetence

The protein and amino acid needs of the immune system are dramatically altered during periods of infection.[28] This is in large part due to the activation of the innate immune system and the production of pro-inflammatory cytokines that aid in nitrogen repartitioning and metabolism.[11]

Inflammatory responses result in negative nitrogen balance and a redistribution of body proteins. Skeletal muscle degradation increases and amino acids are liberated into the circulation and are used for synthesizing protective factors associated with host defense. For example, the liver increases amino acid uptake during infection since this organ synthesizes acute phase proteins involved in host defense.[24] Additionally, rates of protein synthesis are increased in immune tissues due to the increased synthesis of leukocytes.[29] However, the increase in protein synthesis rates in tissues and cell types appears to be driven primarily by specific amino acid needs.[28]

Amino Acids of Importance for Immunity

Arginine can be metabolized to produce nitric oxide (NO) involved in inflammatory responses and polyamines involved in wound healing. In mammals, arginine plays an integral role in the development of B lymphocytes[5] and also regulates the signaling ability of T lymphocytes.[30] Since arginine can be synthesized in ureotelic species, immune cells, particularly macrophages, are capable of synthesizing and recycling arginine for use in nitric oxide production. In uricotelic species and strict ureotelic carnivores that are incapable of arginine synthesis, this amino acid is not only essential, but cannot be recycled.[33] Consequently, this amino acid is of particular importance in these species during periods of infection since increased endogenous synthesis of arginine cannot compensate for increased utilization of this amino acid by the immune system. A considerable amount of research has been conducted in chickens examining the effect of arginine on the immune system,[15,17,35] and the provision of this nutrient to the immune system appears most important for activation.

Glutamine has long been recognized as an important metabolic fuel for the immune system.[2] Glutamine is primarily metabolized to generate energy for leukocytes, as well as reducing equivalents for synthesizing reactive oxygen intermediates.[26] Glutamine can also be metabolized to arginine in murine macrophages for NO synthesis.[25] Though glutamine can be synthesized endogenously, differences in glutamine metabolism between uricotelic and ureotelic species may have implications on glutamine use by cells of the immune system between animals with these nitrogen excretion strategies.

Cysteine can be metabolized to produce glutathione (GSH). GSH is one of the major intracellular antioxidants and its production is regulated by the availability of cysteine. GSH production increases during periods of inflammation,[21] and consequently a greater proportion of cysteine metabolism is directed toward GSH synthesis.[22] GSH plays an important role in leukocyte function and these cells have a strong ability to obtain cysteine.[7] Increased cysteine utilization for GSH synthesis results in taurine production, and inflammatory responses result in increases taurine levels in the liver and kidney. However, taurine levels were reduced in the gastrointestinal tract,[22] and this reduction may have implications on bile salt formation and lipid absorption in carnivores.

Summary

The immune system requires energy and protein/amino acids to protect the host from infectious disease. The energy needs of the immune system differ between innate and adaptive responses and their activation has been shown to reduce performance of other physiological traits, presumably due to competition for energy and nutrient resources. The immune system utilizes amino acids to generate killing compounds and to regulate immune cell function. The energy and protein or amino acid requirements for optimal immunocompetence are not known; however, understanding periods of heightened energy or nutrient need will help to better formulate diets and provide optimal nutritional care to the immune system.

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