TRACE MINERALS AND PIG HEALTH

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INTRODUCTION

For centuries, nutrition has been recognized as important for maintaining animal health. Research has also shown that the nutritional status of an animal does have a profound effect on immune function. Energy, protein, minerals and vitamins all can affect immune status (Beisel, 1982; Wan et al., 1989). These nutrients are also needed to synthesize the organs, tissues, cells and molecules that make up the immune system and are needed by an animal to mount an immune response to a pathogen. Dysfunctions of the immune system result in significant annual losses to livestock producers. Morbidity in animal production systems is a costly economic problem that may, in part, be addressed by nutritional intervention. Not only does morbidity result in medication costs, but also these animals typically grow slower and are less efficient in converting feed to weight gain. An important issue during an immune challenge that is yet to be determined is whether animals that are subjected to immunological stressors have a different nutrient requirement compared to unstressed animals. The nutrient requirements for swine established by the National Research Council (NRC, 1998) are based on experiments that were typically conducted in laboratory facilities or in well controlled research units where environmental and immunological stressors are limited. In addition, the estimated nutrient requirements are set as minimum standards without any safety allowance. According the editors, the requirements listed in the NRC should *not* be considered as recommended allowances (NRC, 1998). Professional nutritionists are cautioned by the editors to consider using increased levels of the more critical nutrients to include "margins of safety" in making formulation decisions. These NRC requirements were determined based on production inputs and not on optimizing immunity or an immune response. At times, enhancing the immune response may be preferred to enhancing performance (i.e. to save the animal from the pathogen). At other times, it may be better to inhibit an immune response. Specific nutrients have been identified that can either enhance or inhibit the immunological response to a pathogen. Animals reared in environments that have different types or levels of pathogens may require more or less of a given nutrient to optimize the immune response. Enhancing the immune response through optimizing trace mineral nutrition and nutrient status is a goal that is receiving increased emphasis.

OVERVIEW OF THE IMMUNE SYSTEM

In order to mount an immune response, whether it is to a foreign antigen that has been given in a vaccine or an antigen from the production environment, an animal needs to have an immune system that is responsive and capable of meeting that challenge. This defense system must attempt to eliminate these harmful challenges or antigens. Specific cells and proteins are produced within an animal to neutralize or destroy these antigens. This is the "acquired immune response" in action.

The immune system can be divided into two categories:

1. Specific Immunity   * cell-mediated and humoral
2. Nonspecific Immunity   * phagocytes, macrophages and neutrophils

Primary lymphoid organs regulate the production and differentiation of these lymphocytes. The cell mediated immune response involves the T-lymphocytes which go through a period of maturation within the thymus, accumulate in lymph nodes and other lymphoid areas, and then are able to respond to a particular antigen in the form of T-cells. The function of T-cells is to help B-cells make antibodies, kill virus-infected cells, regulate the level of immune response and stimulate the microbicidal and cytotoxic activity of other immune effector cells, including macrophages. T-cells have a long life, months to years, which is beneficially responsible for delayed cell-mediated sensitivity.

B-lymphocytes develop in lymphoid tissue before migrating to thymus independent areas to become B-cells. From these B-cells the humoral immune response is derived which involves the production of antibodies. The time of antibody production following the exposure from a particular antigen that is new to the animal is relatively short and will maximize at about ten days. In order to mount an antibody response, most B-cells require the presence of an antigen (T-dependent antigen) together with help from antigen specific T-cells. However, some antigens (T-independent) can directly stimulate B-cells without T-cells. The antibody response is measured as a titer, which will not become very high and persists for a short period of time (two to three weeks). This first antigen response is termed the primary immune response. If this same antigen is again administered, the secondary immune response will be more rapid and result in a higher titer level. This secondary response will usually persist for months.

T-cell and B-cell responses may require days to be fully expressed. The immediate immune defenses of the immune system are the phagocytes, PMN (polymorphonuclear neutrophils) and macrophages. The main function of PMN is the phagocytosis and subsequent destruction of foreign materials. Macrophages belong to the mononuclear phagocytic system. Macrophages are capable of sustained phagocytic activity and they repair tissue by removing dead, dying or damaged tissue.

TRACE ELEMENTS

Trace element deficiencies alter various components of the immune system (Suttle and Jones, 1989). Also, metabolic responses to disease affect trace element metabolism in the animal. Plasma iron and zinc concentrations decrease during the acute phase response, whereas copper concentration increases. Different forms of an element may vary in bioavailability. Bioavailability is defined as the proportion of ingested element that is absorbed, transported to its site of action and converted to a physiologically active form (O'Dell, 1983). Some organic sources of trace elements may have unique absorption and transport mechanisms that are beneficial to the animal (Kidd et al., 1996). Different forms may be used preferentially by the immune system. Research has been published reporting the impact of trace elements, particularly zinc, copper and selenium, on the immune function. The goals of these studies have included determining the concentration and type of trace element to add to the diet to optimize immune function.

Zinc. Zinc is essential to the integrity and function of the immune system. Zinc as a trace element plays an essential role in adequate functioning of the mammalian immune system and has a critical role in maintaining the epithelial tissues lining the body cavities and surfaces. The essentiality of zinc for animals has been known since 1934 (Todd et al., 1934 as cited by Prasad, 1998). The role of zinc in vertebrate homeostasis has mostly come to the attention of scientists because of clinical signs following the deficiency of zinc. Clinical symptoms of zinc deficiency include thymic atrophy and a high frequency of viral, bacterial and fungal infections (Wellinghausen et al., 1997a). The initial indication that zinc might have an impact on the immune system was reported by Kirchner and Ruhl (1970) when they found that zinc could make human peripheral blood mononuclear cells (these include lymphocytes and monocytes) undergo blast transformation and hence act as a mitogen. Since then, zinc has been shown to have an effect on many aspects of immune function (Wellinghausen et al., 1997a). In addition, zinc is an integral cofactor for the optimal activity of over 300 metalloenzymes involved in various major metabolic pathways (Cousins and Hempe, 1990). Zinc-deficient animals show various abnormalities of epithelial tissue dysfunction such as dermatitic conditions, lesions of gastrointestinal tract with damage to the microvilli, feathering problems and increased claw and hoof disease.

The mode of entry of zinc into various cell types is not completely understood. Zinc is taken up by peripheral blood mononuclear cells within minutes and reaches its maximal intracellular concentration within 24 hours (Wellinghausen et al., 1996). Monocytes (macrophages) accumulate more intracellular zinc and have a higher tolerance for it than T-cells. Higher concentrations of zinc (approximately eight times the physiological levels) result in suppressive effects on T-cell proliferation (Wellinghausen 1997b). Therefore, a critical evaluation of plasma zinc levels is important to achieve beneficial effects.

Although the predominant influence of a zinc deficiency is on various T-cell functions, the diversity of the effect is illustrated by a list of functions influenced by zinc deprivation. This includes thymus activity, lymphocyte function, natural killer cell function, antibody dependent cell-mediated cytotoxicity, neutrophil function and lymphokine production. Zinc deficient mice have depressed immune responses to both thymus-dependent and thymus-independent antigens. A 60% reduction in IgG and IgM plaque forming cells in the

spleens of zinc deficient mice was observed in response to sheep red blood cells (a thymus dependent antigen) as compared to zinc adequate mice (Fraker, 1983). Decreased zinc levels reduce natural killer cell activities and down-regulate phagocytic activity of macrophages and certain functions of neutrophils (Wellinghausen et al., 1997b). Zinc induces interleukin-1 (IL-1), IL-6 and TNF-α in peripheral blood mononuclear cells and thus zinc has immunoregulatory capacity (Driessen et al., 1994). Scott and Koski (2000), using a zinc-deficient model of mice, showed reduced production of IL-4 in the spleen which in turn resulted in reduced IgE, IgG and eosinophils. They concluded that zinc deficiency has a profound effect on the gut mucosal immune response and can prolong the parasite survival. However, the major impact of zinc deficiency is on the cell mediated immune function. Zinc is an essential cofactor for the thymic hormone thymulin and even a mild deficiency of zinc can cause significantly reduced levels of thymulin that could be corrected by zinc supplementation (Prasad et al., 1988). Thymulin binds to high affinity receptors on T-cells, induces several T-cell markers, and promotes T-cell functions such as cytotoxicity, suppressor function, and interleukin-2 (IL-2) production (Prasad, 1998). Zinc deficient individuals have inactive thymulin in serum and supplementation can activate it restoring the T-cell function (Prasad et al., 1988). Another aspect of effects of zinc deficiency on T-cells is an imbalance of Th1 and Th2 functions. In a study with human subjects, production of interferon-γ (IFN-γ) was decreased, and the production of IL-4, IL-6 and IL-10 was not affected by a zinc deficiency (Beck et al., 1997a). Production of TNF-α by peripheral blood mononuclear cells was also reduced. These results suggest that zinc deficiency affects mainly the Th1 functions. In addition, zinc deficiency results in a decrease in $CD4^+$ to $CD8^+$ ratio and this can be corrected by zinc supplementation (Beck et al., 1997a; Prasad et al., 1997). Thus zinc appears to be involved in the generation of new $CD4^+$ T-cells. In humans, zinc deficiency results in a decrease in $CD8^+$, $CD73^+$ T-lymphocytes which are precursors to cytotoxic T lymphocytes (Beck et al., 1997b). Thus decreased thymulin activity, reduced NK cell activity, imbalance of Th1-Th2 function, and reduced numbers of cytotoxic T cells might contribute to increased susceptibility of zinc deficient patients to infections.

Copper. The primary physiological role of copper is its function as an enzyme activator and enzyme constituent. Copper is a key component of the immune system and has a basic role in iron metabolism and red blood cell maturation. The liver is the central organ of copper metabolism. Anemia is a common expression of severe or prolonged copper deficiency. Copper has also been shown to promote feed intake in animals. Copper absorption is affected by other components within a ration (iron, sulfur and molybdenum). A strong antagonism between copper and zinc has been clearly established in numerous animal experiments. The interaction between copper and calcium appears to be very complex. Dietary calcium has been shown to reduce the absorption of copper in mice, while enhancing copper toxicity in pigs. The interaction of copper and iron is observed in the requirement of copper for proper iron utilization. Copper is an essential component of several metalloenzymes (copper metallothionein, cytochrome c oxidase, Cu,Zn-superoxide dismutase, ceruloplasmin and dopamine-α-monoxygenase) that are critical for normal growth and development.

Copper also has a role as an important component of the immune system. Two copper containing enzymes, ceruloplasmin and superoxide dismutase, have been shown to exhibit anti-inflammatory activity. Thus like zinc, copper can be considered to have strong effects on the immune system. Copper deficiency has been shown to cause a basic T-lymphocyte defect reflected by increased susceptibility to T-cell mediated infections. In copper deficient pigs, lymphocyte blastogenic responses to phytohemagglutinin and concanavalin A were reduced (Bala et al., 1992). The mechanism by which copper acts in altering immune responses may involve an interaction at the level of the plasma membrane. Copper has been shown to ameliorate the toxic effects on both T-cells and PMN leukocytes. It also has been shown that copper is involved in the structure of immunoglobulins. Although many aspects of the role of copper in host defense remain to be investigated, preliminary results indicate the potential for a significant interaction.

Selenium. Prior to 1957, the nutritional significance of selenium was related to its toxicity. Today, selenium is recognized as an essential element that defends the body against oxidative stress. Selenium was established as an essential nutrient for mammals in 1957, but it was not until the early 1970's that a true biological function for selenium was recognized (Schwartz and Foltz, 1957; Rotruck et al., 1972). Selenium has been shown to affect health in many species. However, the nutritional requirements and mechanisms of action remain poorly defined. Selenium is a component of glutathione peroxidase, an important antioxidant (Rotruck et al., 1973). The first indication that selenium might play a role in immunity was shown by the accumulation of Selenium-75 in dog leukocytes (McConnell, 1959). The first evidence that selenium could affect the immune response came from studies where selenium enhanced the humoral immune response in

mice (Spallholz et al., 1973a,b). In mice challenged with sheep red blood cells, selenium supplementation at 1 to 3 ppm selenium increased IgM and IgG antibody titer responses and increased IgM antibody forming cells. In sows, selenium deficiency decreased the phagocytic and microbicidal activity of neutrophils (Wuryastuti et al., 1993). Glutathione peroxidase may be needed indirectly along with glutathione reductase to provide NADPH for the respiratory burst. If the respiratory burst were compromised, there would be reduced free radical generation, and thus decreased killing capacity in selenium-deficient neutrophils (Suttle and Jones, 1989). Selenium appears to be very important as an antioxidant and as a factor in the energy metabolism of phagocytic cells but the mechanism of its modulation of humoral immunity remains speculative.

Iron. Both cell mediated and humoral immunity are compromised in iron deficient animals. Studies indicate that iron deficiency may have both augmenting and inhibitory effects on host defense mechanisms, with the ultimate result being dictated by the relative influence of the many pathways in which iron plays a role. While studies indicate an iron deficiency is associated with immune dysfunction, conditions associated with excess iron have been demonstrated to be immunomodulatory. Excessive serum iron may contribute to the virulence of certain iron-dependent bacterial pathogens by promoting their growth.

Manganese. Manganese is essential for normal brain function, and plays a role in enzyme systems, collagen formation, bone growth, urea formation, fatty acid and cholesterol synthesis, and digestion of protein. In addition, it plays an important role in reproduction. There is little evidence that manganese plays a major role in immunological function. It has been reported to increase antibody titers and other nonspecific resistance factors in certain animals. Rats marginally deficient in manganese showed lower IgG agglutinins and a fraction of gamma globulins. Interaction of manganese with neutrophils and macrophages has also been demonstrated.

Chromium. Chromium potentiates insulin action, resulting in increased uptake of glucose and amino acids by cells in the body (NRC, 1997, 1998). Signs of a chromium deficiency include reduced growth rate, reduced feed efficiency and reduced immune function (Puls, 1994; Stoecker, 1990). Supplementing chromium to swine has been shown to increase muscling and reduce fat thickness. Very little data are available showing an effect of chromium on immune function. Four of eight studies with stressed calves have shown significant beneficial effects of supplemental organic chromium on morbidity and/or growth (NRC, 1997). However, one study with weaning pigs reported inconsistent effects of supplemental chromium on immune status (van Heugten and Spears, 1997).

SUMMARY

Changes in trace mineral nutrient supply can significantly influence the immune system. First, the nutritional status of the animal can dramatically affect the degree of proliferation of immune cells and immunogenic molecules, as certain nutrients are needed as substrates for these cells and molecules. In addition, some nutrients are needed as substrates for intra- and inter-cellular communication. Second, nutrient status of the developing embryo has profound effects on the immune system development. Parental nutrient status affects the availability and supply of nutrients that are needed for the proper development of the embryo. Third, just as production animals require dietary nutrients, invading pathogens need nutrients for replication *in vivo*. Pathogens are dependant on the host for most nutrients and therefore host nutrient status affects the duration and intensity of an immune response. Nutritional modulation of the immune system can be used to ensure appropriate function during an immunological challenge.

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