Effects of Immune Activation on Nutrition and Production Efficiency

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INTRODUCTION

The relationship between immunity and metabolism has been realized to be very complex and interconnected. Traditional thinking is that activation of the immune system represents a significant nutritional demand that competes with productive processes such as protein and milk synthesis. Dogma states that this drain of nutrients is the cause for decreased productive efficiency of livestock animals during sickness. Although there is no doubt that productive efficiency is decreased during morbidity, the reason behind this decrease in efficiency likely much more of a coordinated response rather than a competition for substrates. Many underlying metabolic adaptations occur to support immune function during periods of sickness such that variables important to livestock production systems (i.e., growth, reproduction, lactation, or metabolic health) are compromised despite the presence of seemingly sound dietary formulation.

INTEGRATION OF IMMUNE FUNCTION AND METABOLISM

Infection occurs when a population of invading pathogens (i.e., bacteria, viruses, protozoa, etc.) becomes established within another living organism. Infections of the respiratory or digestive tracts are common in growing animals, and additionally, infections of the mammary gland (mastitis) or uterus (metritis) are common sources of inflammation in lactating dairy cows. Other health disorders common during the periparturient period in dairy cows (e.g., milk fever and ketosis) do not directly arise from infectious organisms, but instead have metabolic origins.

During infection, a pathogen gains entry through the physical or mucosal barriers of the animal and becomes established within the tissue. Certain white blood cells, or leukocytes, of the immune system [including macrophages, monocytes, and polymorphonuclear neutriphils (PMN)] serve as sentinels for the animal and become activated when they come in contact with these "non-self" pathogens. Upon activation, leukocytes secrete signaling molecules that support the immune response called proinflammatory cytokines. The proinflammatory cytokines include tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1), and interleukin-6 (IL-6); however, numerous other cytokines exist to support the immune response as well. These cytokines are initially secreted by leukocytes at the site of infection where they act locally to activate other immune cells.

In addition to their effects on leukocytes, cytokines also have effects outside of the "traditional" immune system because metabolic tissues have functional receptors for these signaling molecules of the immune system. For example, the proinflammatory cytokines have direct effects on such metabolic tissues as the brain, skeletal muscle, adipose tissue (fat), liver, and endocrine glands (Johnson, 1997). Klasing (1988) reviewed the impacts of cytokines on metabolism and reported that feed intake, protein metabolism, fat metabolism, carbohydrate

metabolism, mineral metabolism, and endocrine secretions were all affected by inflammation. Furthermore, secondary effects of immune activation also occur via classical metabolic endocrine regulation due to changes in endocrine gland secretions (Waldron et al., 2003; Waldron et al., 2006).

Further complicating the relationship between immune function and metabolism, it is now clear that not only do metabolic tissues respond to signals from the immune system, in many cases "metabolic" tissues actually produce and secrete immune-related molecules as well. Far from an exclusive list, it is has now been shown that mammary epithelial cells produce several acute-phase proteins and cytokines including TNF-α and interleukin-8 (Wellnitz and Kerr, 2004); the liver produces antimicrobial peptides (Sang et al., 2006) and acute-phase proteins and cytokines (Loor et al., 2005), the anterior pituitary gland produces among others, IL-6 and prostaglandins (Abraham et al., 1998); and fat cells (adipocytes) produce such a wide range of immune-related molecules (including membrane-bound TNF-α, IL-6, resistin, etc.) that these molecules have been termed adipocytokines or adipokines (Hutley and Prins, 2005).

Completing the relationship between immune function and metabolism, it has also been reported that multiple nutrients and metabolites influence immunity. The role of dietary nutrients in supporting immune function has received significant research attention. Vitamins (e.g., vitamins C, D, and E) and trace minerals (e.g., zinc or selenium) are all familiar to us from advertisements touting the role of these nutrients in human health and disease. Furthermore, at least basal levels, and in some cases supranutritional levels, of these nutrients have been shown be supportive for animal health in livestock production systems (Spears and Weiss, 2008; Spears, 2000; Weiss, 1998). Other nutrients such as specific fatty acids have been studied for their ability to influence immune function (Calder, 2006) and hold promise for future use in livestock species.

EFFECTS OF IMMUNE ACTIVATION ON GROWTH

Sick animals grow more slowly than do healthy animals (Johnson, 1997; Spurlock, 1997). Reduced growth is a result of both changes in traditional endocrine hormones and also an effect of proinflammatory cytokines directly on metabolic tissues. Infection or inflammation results in decreased feed intake, but the reduction in growth caused by immune activation is often greater than can be explained by changes in feed intake alone (Tracey et al., 1988). In addition to decreased feed intake, immune activation in many species has resulted in GH resistance, or an apparent uncoupling of the somatotropic axis; that is, increased serum GH concentrations were not accompanied by changes in serum IGF-1 concentrations, or no change in growth hormone was associated with a decrease in plasma IGF-1 concentration. Spurlock (1997) also reported uncoupling of the somatotropic axis in immune challenged pigs such that administration of exogenous somatotropin did not prevent reductions in circulating IGF-1 concentrations. Investigations of immune-triggered uncoupling of the somatotropic axis in laboratory animals suggest that cytokines alter GH receptor signaling and subsequent expression of the acid-labile subunit of IGF-1 (Mao et al., 1999; Boisclair et al., 2000). Another aspect of the somatotropic axis that may influence trophic activities is the concentration of IGF binding proteins after immune activation. Changes in binding proteins such as those reported in calves (Elsasser et al., 1995) and sheep (Briard et al., 2000) could tissue-specifically affect the

metabolic influence of IGF-1, even without changes in plasma IGF-1 concentrations. Davis (1998) postulated that uncoupling of the somatotropic axis may indirectly play a role in the immune response by partitioning nutrients away from productive tissues (e.g., skeletal muscle or mammary gland) for subsequent use by the immune system and directly, by positive actions of GH on the immune system. Indeed GH has been shown to enhance immune function in healthy and diseased cows (reviewed by Burvenich, et al., 1999).

Alterations in the somatotropic axis discussed above, in addition to other endocrine changes and the direct effects of cytokines on metabolic tissues are responsible for changes in net protein deposition. Klasing and Austic (1984a,b) reported that immune activation resulted in changes in both, protein synthesis and degradation rates such that the net effect was decreased muscle mass gain. The reason for the increased protein catabolism relative to synthesis is uncertain; however, it has been hypothesized that the increased efflux of amino acids from skeletal muscle are shunted to the liver to support the immune response and are necessary to make up for the decreased intake of amino acids in feed, the increased need of the liver for gluconeogenic amino acids, and the significant amount and changed profile of amino acids needed for acute phase protein synthesis compared to the normal (non-inflammatory) hepatic proteins (Spurlock, 1997; Reeds et al., 1994).

EFFECTS OF IMMUNE ACTIVATION ON LACTATION

Immune activation results in dramatic changes in circulating concentrations of cytokines and hormones in the blood. These alterations in endocrine profile, and cytokines themselves, cause a marked decreased milk production in lactating cows (Rajala-Schultz et al., 1999; Shuster and Harmon, 1992; Shuster et al., 1991a). Decreased milk synthesis is not due simply to decreased feed intake associated with sickness because healthy cows that were pair-fed to acutely mastitic cows displayed normal milk production while their mastitic counterparts decreased milk production by up to 70% (Waldron et al., 2006). Lohuis et al. (1990) reported the loss of total daily milk production of cows was related positively with areas under the curves of heart rate, rumen amplitude, and counts of E. coli in secreta from inoculated quarters. The decreased milk production due to mastitis is mediated by multiple pathophysiological events and is not solely due to inflammatory damage in the mammary epithelium. Part of the reduced lactational performance may result from escape of milk components from the udder into the circulation (Shuster et al., 1991b). Reduced lactational performance is not mediated by the acute cortisol increase associated with inflammation (Shuster and Harmon, 1992) or by reduced concentrations of growth hormone or IGF-1 (Shuster et al., 1995). These authors also noted that inflammatory cytokines are produced at a time consistent with a possible role in the inhibition of milk synthesis (Shuster et al., 1995). The positive effects of growth hormone on milk production and recovery from coliform mastitis may be due to the enhanced function of neutrophils resulting in a better defense of the mammary gland (Burvenich et al., 1999).

EFFECTS OF IMMUNE ACTIVATION ON PERIPARTURIENT METABOLIC HEALTH

Periods of negative energy balance in livestock species, including the early-lactation period of dairy cows, are marked by the mobilization of lipid stores and increased circulating

concentrations of nonesterified fatty acids (NEFA) in blood. As such, the plasma NEFA concentration is a good indicator of energy balance in healthy, un-stressed animals. Although dry matter intake is significantly reduced during periods of inflammation, the activity of pro-inflammatory cytokines in dampening synthesis in productive tissues, allows for the animal to remain in apparent positive energy balance during short periods of inflammation (Figures 1-3; Waldron et al., 2006). Furthermore, despite the requisite use of glucose by leukocytes of the innate immune system, plasma glucose concentration was maintained during experimental mastitis in early-lactation dairy cows (Waldron et al., 2006). Estimates in poultry suggest that immune activation results in increased total energy and protein utilization of 4-5% (Klasing, 2004). However, apparently the decrease in productive tissue synthesis offsets this increased demand (Table 1) to allow the animal to effectively fight infection and maintain metabolic health. This balancing of energy metabolism clearly represents coordination of the immune and metabolic systems with no evidence of competition, at least during the short-term. Although energy metabolism appeared to be well-managed in these animals, further quantitative study during longer periods of inflammation is warranted.

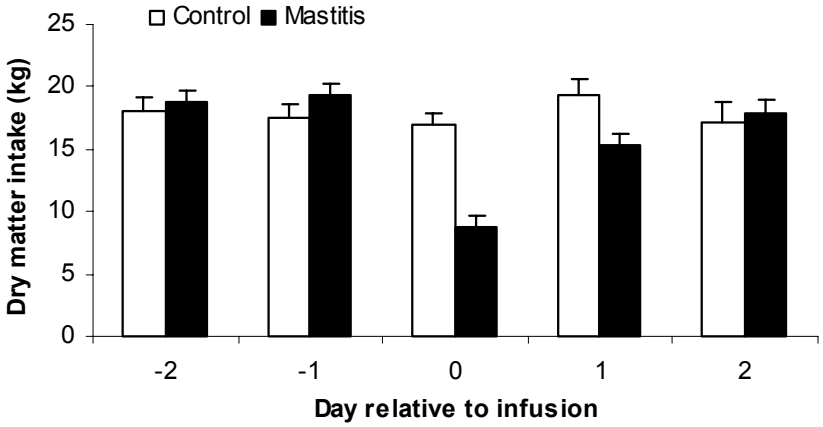

Figure 1. Daily dry matter intake following intramammary lipopolysaccharide (to cause mastitis) or saline infusion into early-lactation dairy cows[a]. Experimental mastitis was induced approximately 4 hours after morning feeding on day zero relative to infusion.

[a] treatment by time effect, $P < 0.01$

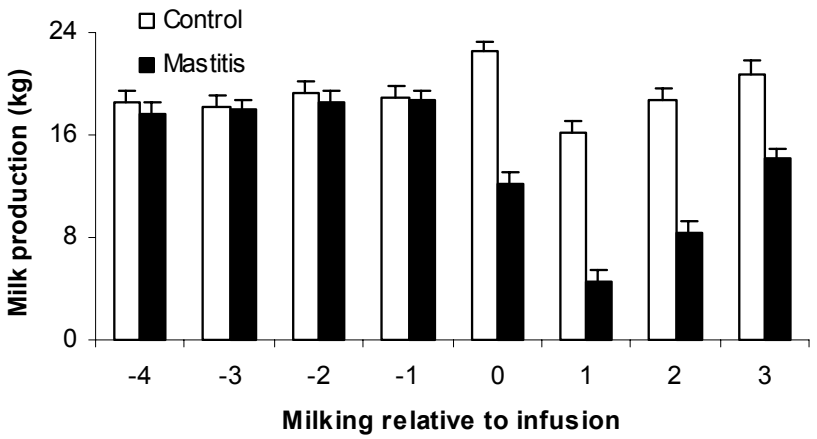

Figure 2. Milk production at each milking following intramammary lipopolysaccharide (to cause mastitis) or saline infusion into early-lactation dairy cows[a]. Experimental mastitis was induced approximately 4 hours after morning milking and 10 hours before evening milking on day zero relative to infusion.

[a] treatment by time effect, $P < 0.01$

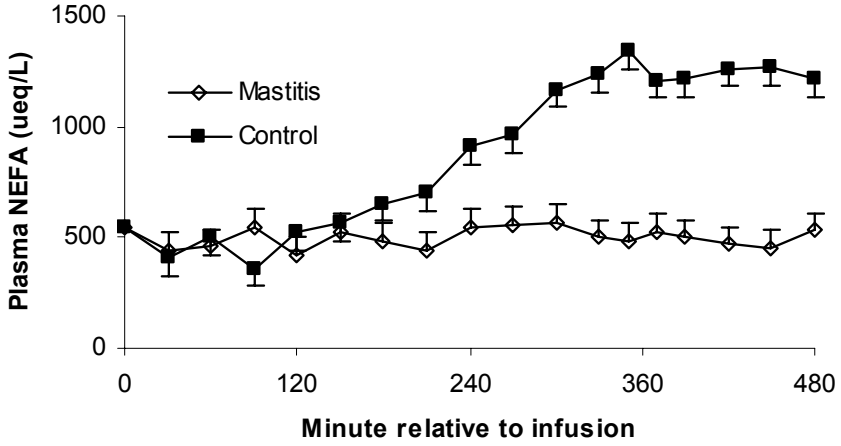

Figure 3. Plasma nonesterified fatty acid (NEFA) concentration following intramammary lipopolysaccharide (to cause mastitis) or saline infusion into early-lactation dairy cows[a]. Means were adjusted by analysis of covariance using the mean NEFA concentration for each treatment group from –240 through 0 minutes relative to intramammary infusion.

[a] treatment by time effect, $P < 0.01$

Table 1. Calculated metabolizable energy (ME, Mcal) requirements following intramammary lipopolysaccharide (to cause mastitis) or saline infusion into early-lactation dairy cows.

	Mastitis Cows (ME, Mcal)	**Control Cows** (ME, Mcal)
Maintenance	8.9	9.0
Milk Synthesis	14.6	31.0
Fever	1.1	--
Estimated Immune Costs	1.2	--
	25.8	40.0

PRACTICAL RECOMMENDATIONS

It is evident that the effects of nutrition and immunity are interrelated. Nutritional physiology impacts immune function and immune activity alters metabolism. At this time, specific recommendations to optimize nutritional immunology are difficult because research is lacking. Our current nutritional recommendations are based on the amount of a given nutrient that will result in no deficiency symptoms for the nutrient and maximizes productive processes (e.g., growth, milk production) - the amount of that same nutrient that maximizes immunity may be very different. Obviously, the best way to minimize the negative effects of immune activity on nutrition and metabolism is to minimize the occurrence and severity of infection and inflammation in livestock production systems. Unfortunately, we have little peer-reviewed research to support specific nutritional recommendations to maximize immunity, and most of our efforts to minimize immune activation will be management oriented. At this time, our best recommendations in feeding for optimal nutritional immunity are concept-based. That is, we don't know the specific requirements yet, but we are beginning to understand some of the nutrients that impact immune function, and we can therefore nutritionally manage the animal to optimize those nutrients and/or metabolites. For example, we know that many trace minerals and vitamins are important in immune function. We don't know what level of these nutrients maximizes immunity, but we do know that deficiencies impair immunity. Therefore, we strive to meet or exceed National Research Council requirements with these nutrients coming from high quality sources. Another example of concept-based feeding regards managing the periparturient dairy cow to minimize negative energy balance. We know that excessive plasma NEFA and ketone-body metabolism can impair immunity, therefore we must attempt to manage the animal such that plasma NEFA and BHBA concentrations remain at moderate levels. To accomplish this we can incorporate the same strategies as those to maximize metabolic health in fresh cows – namely, balanced pre- and post-calving diets, watching for changes in the forage base that will result in nutritional imbalances, excellent feeding management, monitoring fresh cows to identify potential problems quickly, and minimizing stress on these animals.

SUMMARY

Immune activation impacts nutrition, metabolism, and production efficiency. Pro-inflammatory cytokines secreted during an immune response directly act on metabolic tissues and endocrine glands to affect metabolism and hormone action. Synthesis in productive tissues is thus directly attenuated. Indeed, the effects of immune activation on metabolism are a coordinated response, not simply competition for substrates. During a short-term immune response, the animal appears to effectively manage energy metabolism. However, mineral and vitamin metabolism may frequently be suboptimal, even during short-term inflammation. Physiological state and nutrient status prior to immune activation appear to be important for effective immunity.

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