Nutrition and Immunity

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Summary

Nutrition has been known to impact animal immunity for some time, but recent data have demonstrated important impacts of the immune system on metabolism. This cross-talk, mediated by absorbed nutrients, intermediary metabolites, and inflammatory compounds, is especially prevalent during the transition to lactation. A clearer picture is emerging at the mechanistic level to explain why cows with metabolic disorders are more prone to infections and vice-versa. Nutritional strategies that control body condition in dry cows, provide adequate dietary antioxidants, and use bioactive nutrients to influence inflammatory signals can help to limit disease incidence during the transition period.

Introduction

Until the last 15 years, the connections between nutrition and immunity were considered somewhat limited. It was understood that nutrients served as critical substrates for certain processes in the immune system, and in times of severe inflammation, there were obvious impacts on metabolism, but little else was known. An accelerating field of research has now demonstrated that immune cells are directly involved in a surprising array of metabolic functions, including maintenance of gastrointestinal function, activation of adipose tissue lipolysis, and regulation of insulin sensitivity in multiple tissues. Likewise, mechanisms have been discovered which link nutrients, such as saturated fatty acids, calcium, selenium, vitamin D, volatile fatty acids, ketone bodies, and omega-3 fatty acids, to altered function of immune cells. The vast number of bidirectional cross-links between the metabolic system and the immune system has fundamentally altered our view of physiology, especially during times of stress.

Recent research in dairy cattle has highlighted the role of systemic inflammation in infectious diseases and has suggested that inflammation is involved in metabolic diseases as well. A key role for inflammation in numerous transition cow disorders may help to explain links between these diverse conditions. On the other hand, inflammatory pathways play important roles in normal immune function, metabolism, and reproduction. An improved understanding of the necessary and pathological aspects of inflammatory pathways in transition cows may improve our ability to predict and prevent transition disorders.

Inflammatory Responses to Infection

During infections, such as mastitis or metritis, immune cells in the body recognize invading pathogens and become activated. When the infection is caused by Gram-negative bacteria, lipopolysaccharide **(LPS)** released by the bacteria also activates immune cells. The activation of local and systemic host defense mechanisms requires cross-talk between numerous types of immune cells, and one component of this response is inflammation.

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The host of signaling molecules released by activated immune cells includes inflammatory mediators, such as nitric oxide, prostaglandins, and cytokines. Whereas many of these molecules promote local inflammation and increased blood flow to the infected tissue, inflammatory cytokines play a key role in stimulating systemic inflammatory responses, including increased body temperature, increased heart rate, and decreased feed intake. Cytokines are able to alter many physiological systems because nearly all cell types express cytokine receptors. Key inflammatory cytokines include tumor necrosis factor alpha **(TNFα)**, interleukin **(IL)** 1β, and IL-6; these inflammatory cytokines act through many of the same signaling cascades and often produce similar responses in cells.

One effect of cytokines is to activate production of acute phase proteins. Primarily produced by the liver, this class of proteins includes haptoglobin, serum amyloid A, and C-reactive protein. Proteins that participate in the acute phase response to infection are generally found in very low abundance in the bloodstream, but they are greatly elevated during systemic inflammation. The importance of acute phase proteins in the response to infection is somewhat unclear, but they have gained widespread acceptance as markers of inflammation.

It is clear that mammary and uterine infections result in both local and systemic inflammation. Coliform mastitis results in release of LPS into the bloodstream and increased plasma concentrations of cytokines and acute phase proteins (Hoeben et al., 2000). Likewise, metritis is associated with an acute phase response in transition cows (Huzzey et al., 2009); in fact, plasma haptoglobin is elevated prior to clinical signs of metritis. Furthermore, monocytes are known to become more responsive to inflammatory stimulants during the transition period, resulting in greater secretion of inflammatory cytokines when stimulated (Sordillo et al., 1995). Mastitis and metritis can therefore result in systemic inflammation.

Is There a Role for Inflammation in Metabolic Disorders?

Inflammation has been proposed as a missing link in the pathology of metabolic disorders in transition cows (Drackley, 1999). Recent findings have documented relationships between inflammatory mediators and metabolic disorders. Plasma concentrations of haptoglobin and serum amyloid A were increased in cows that developed fatty liver (Ametaj et al., 2005), and Ohtsuka et al. (2001) observed increased serum TNFα activity in cows with moderate to severe fatty liver. A retrospective study of cows on 3 commercial Italian dairy farms suggested that liver inflammation is associated with a problematic transition to lactation (Bertoni et al., 2008). Cows were classified in quartiles for degree of liver inflammation based on plasma concentrations of acute phase proteins. Those cows with the strongest inflammatory profiles were at 8-fold greater risk for experiencing one or more transition disorders, had lower plasma calcium concentrations, took longer to re-breed, and produced less milk in the first month of lactation (Bertoni et al., 2008). These correlations have driven strong interest in potential mechanisms underlying an inflammation-based pathogenesis of transition cow disorders.

Inflammatory Pathways That Alter Nutrient Metabolism

Inflammatory cytokines

Consistent with their role in responses to infection, cytokines generally have catabolic effects on metabolism. Cytokines promote the breakdown of fat stores through decreased feed intake, impaired insulin sensitivity, and direct stimulation of lipolysis. All of these conditions are associated with ketosis and fatty liver in dairy cattle. Inflammatory cytokines also directly alter metabolic function of the liver. For example, TNFα decreases liver glucose production in some scenarios (Kettelhut et al., 1987) and

promotes triglyceride accumulation once mobilized non-esterified fatty acids **(NEFA)** reach the liver (García-Ruiz et al., 2006). Triglyceride accumulation is likely due in part to decreased fatty acid **(FA)** oxidation in the liver after exposure to TNFα (Nachiappan et al., 1994). The TNFα also decreased production of apolipoproteins (Ettinger et al., 1994), which may impair triglyceride export in very low density lipoproteins **(VLDL)** and contribute to hepatic triglcyeride accumulation. Adipose tissue is a key source of circulating cytokines in obese animals of several species, but some recent evidence suggests that chronic release of cytokines by adipose tissue in transition cows may be minimal (Schoenberg et al., 2011). Nevertheless, cytokine signaling in cows with clinical infections may provide a critical "first strike" of liver inflammation.

Oxidative stress

Lipid peroxides are also emerging as likely mediators linking plasma lipids to inflammation. Lipid peroxides are produced when intracellular lipids encounter reactive oxygen species **(ROS),** such as hydrogen peroxide. Some ROS are always produced in the liver; however, events occurring in early lactation likely contribute to enhanced ROS production. One adaptation to increasing delivery of NEFA to the liver in early lactation is an increase in the capacity of peroxisomal oxidation (Grum et al., 1996), an alternative pathway for FA oxidation. Enhanced peroxisomal oxidation increases total oxidative capacity of the hepatocyte. However, the first step in this pathway produces hydrogen peroxide rather than nicotinamide adenine dinucleotide **(NADH)**, and therefore, it contributes to ROS production to a greater extent than mitochondrial oxidation. Increased ROS production in early lactation cows, coupled with increased NEFA concentration, increases lipid peroxide formation; both the transition to lactation and high body condition are associated with increased plasma markers of lipid peroxidation (Bernabucci et al.,

2005). Similar mechanisms may underlie the fact that withdrawal of feed and water for just 24 hours induced an acute-phase response in steers (Cappellozza et al., 2011).

In vivo observations support a role for oxidative stress in metabolic disorders. Dairy cows with fatty liver have lower antioxidant status and higher hepatic lipid peroxide concentrations than healthy cows (Mudron et al., 1999). Despite these data suggesting a metabolic effect of oxidative stress, transition cow studies employing antioxidants as treatments have looked almost exclusively at effects on infectious disorders, such as mastitis and metritis. In rodent models, however, studies have demonstrated that antioxidants improve metabolic function in animals challenged with high-fat diets (Mao et al., 2010) and endotoxin (Sakaguchi and Furusawa, 2006). In a recent phase 3 clinical trial, vitamin E supplementation significantly improved liver health in steatohepatitis patients compared to placebo (Sanyal et al., 2010).

LPS translocation from the gut

Toll-like receptor 4 **(TLR4)** was initially identified as a protein expressed in immune cells that is critical for inflammatory responses to LPS (Poltorak et al., 1998). There is now growing recognition that TLR4 is expressed in many cell types, including muscle cells, adipocytes, and hepatocytes. Although immune cell-dependent mechanisms have been shown to alter liver function (Saberi et al., 2009), direct activation of TLR4 in hepatocytes can also influence metabolism.

It has long been debated whether acidosis promotes release and translocation of LPS from the rumen and into the bloodstream. Khafipour et al. (2009) nicely demonstrated that induction of sub-acute ruminal acidosis increased both ruminal and plasma LPS concentrations. This treatment also significantly elevated plasma concentrations of acute-phase proteins, presumably mediated by

TLR4 sensing of the translocated LPS. Although no indices of hepatic metabolism were measured in this study, it is likely that if LPS was sufficiently elevated to induce an acute phase response, expression of metabolic genes was also altered. Studies in other species suggest that numerous physiological stressors, including heat stress, can disrupt tight junctions between gastrointestinal epithelial cells and allow translocation of LPS (Lambert, 2009). If this phenomenon is common in dairy cattle, it may play a significant role in metabolic responses to parturition, heat stress, diet transitions, and other stressors.

Net Effects of Inflammation on Metabolism of Lactating Cows

Strong evidence has emerged from 2 recent studies where inflammatory mediators directly induced metabolic problems. Trevisi et al. (2009) orally administered interferon-α (a cytokine) daily during the final 2 weeks of gestation, which caused liver inflammation and release of acute phase proteins. Compared to control cows, treated cows had significantly higher plasma ketone concentrations in the first 2 weeks after calving. Our own lab recently reported that subcutaneous injection of TNFα for 7 days doubled liver triglyceride content in late-lactation dairy cows (Bradford et al., 2009). We also observed changes in mRNA abundance, consistent with transcriptionally-mediated increases in FA uptake and esterification and decreased FA oxidation. These results strongly support the hypothesis that inflammation disrupts normal metabolism, because although both of the above treatments were considered low-dose and short-term, they nevertheless promoted ketosis and fatty liver, respectively.

Our lab recently completed a study in which 78 transition cows were alternately provided with drinking water containing either 0 or 1.68 g/L sodium salicylate for the first 7 days postpartum (Farney and Bradford, unpublished). Consistent with our hypothesis, cows treated with sodium salicylate tended to produce 9% more energy-corrected milk by week 3 of lactation, with no overall differences in feed intake or incidence of metabolic or infectious diseases. However, the production response was driven primarily by an increase in milk fat content among the salicylate-treated cows, and metabolic profiling revealed that these cows had sustained elevations of plasma NEFA and ketone concentrations compared to control cows. These findings suggest still more complicated roles of inflammatory pathways; it may be that low-level inflammation provides a "release valve" for the metabolic system, allowing the cow to slow the rate of lipolysis and ketogenesis even as negative energy balance continues, albeit at the risk of impairing liver function. These findings have reminded us that many effects in biology are not linear; it may well be that elevated inflammatory signaling impairs metabolism but that suppression of basal inflammatory signals also has negative effects.

The Other Side of the Coin: Nutrients Influence Immune Function

A number of excellent reviews have discussed a variety of nutrients that impact immune function, and readers are referred to these for a broader context (Goff, 2006; Spears and Weiss, 2008; Contreras and Sordillo, 2011).

To illustrate the importance of metabolic function on immune response, it is interesting to consider the effects of beta-hydroxybutric acid **(BHBA)**, the primary ketone body in the bloodstream. Much evidence has accumulated demonstrat-ing epidemiological links between ketosis and infectious disorders. For example, ketosis was the most significant risk factor for endometritis in a study of nearly 800 cows (Cheong et al., 2011). Elevated BHBA in the first 3 days after calving was a significant predictor of mastitis risk in the first month of lactation (Jánosi et al.,

2003), and ketotic cows experienced more severe disease after intramammary *E. coli* administration (Kremer et al., 1993). Simply put, ketotic cows are at significantly greater risk of subsequently developing mastitis (Oltenacu and Ekesbo, 1994) and endometritis (Duffield et al., 2009).

In addition to epidemiological links between ketosis and infectious disorders, mech-anistic studies have demonstrated that ketones directly impair a number of functions of immune cells. Among other findings, in vitro administration of BHBA decreases viability of and phagocytosis by macrophages (Cerone et al., 2007), neutrophil migration (Sartorelli et al., 1999; Cerone et al., 2007), and phagocytosis and pathogen killing by neutrophils (Sartorelli et al., 1999). The broad effects of physiological concentrations of BHBA on a variety of immune cells *in vitro* clearly demonstrate that BHBA can directly impair immune function.

Connecting this piece with the effects of inflammatory mediators on metabolism completes a pathological feedback loop promoting a disease complex which can spiral out of control (Figure 1). An immune system partially incapacitated by elevated ketones is less likely to rapidly clear a pathogen that gains access to, for example, the uterus. This results in a sustained infection which, even if it is subclinical, causes a prolonged release of inflammatory compounds into the circulation. The resulting inflammation disrupts normal metabolic function of the liver, potentially promoting even greater production of ketone bodies. Although this downward spiral can clearly be resolved in some cows (particularly with antibiotic treatment or ketosis interventions), this sort of cross-talk likely underpins some of the well-recognized links between various, seemingly unrelated, transition disorders.

Nutritional Strategies to Promote Transition Health

Antioxidants

Dietary antioxidants, notably vitamin E and selenium, are important for their ability to contribute to ROS neutralization, thereby impeding the progression toward inflammation. Interestingly, plasma concentrations of a-tocopherol (vitamin E) decrease through the transition period (Weiss et al., 1990a), and low antioxidant status is associated with transition cow disorders (Mudron et al., 1997; LeBlanc et al., 2004). Supplementing vitamin E prepartum improves antioxidant status (Weiss et al., 1990a). Given the importance of antioxidants in modulating inflammation, it is not surprising that multiple studies have shown that supplementing vitamin E in excess of traditional recommendations decreases the incidence and severity of clinical mastitis (Smith et al., 1984; Weiss et al., 1990a). More recently, a meta-analysis showed that supplemental vitamin E is also effective at preventing retained placenta (Bourne et al., 2007).

Low plasma vitamin E concentrations are associated with increased incidence of fatty liver and displaced abomasum (Mudron et al., 1997). Surprisingly, no published studies have evaluated the effects of supplemental vitamin E on liver metabolism or incidence of metabolic disorders. Given that supplemental vitamin E can decrease inflammatory cytokine production (Poynter and Daynes, 1998) and improve liver antioxidant status in mice with fatty liver (Soltys et al., 2001), supplemental vitamin E may improve liver function in transition cows. Beta carotene, a precursor of vitamin A, can also function as an antioxidant (Spears and Weiss, 2008), and concentrations of both vitamin A and β-carotene typically decrease during the transition period (LeBlanc et al., 2004).

Although much of the literature on antioxidants in transition cows demonstrates positive

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effects, these nutrients must be used with caution. In an effort to maximize the odds of observing a response, most studies are designed with rather dramatic treatments; for example, one classic study (Weiss et al., 1990b) compared vitamin E intakes of 574 IU/day (no supplemental vitamin E) to 1474 IU/day (supplementing 88 IU/lb dry matter). In many such scenarios, the control group is fed a diet that is marginally deficient in the nutrient of interest. On most dairy farms, this is not the case. As a result, adding large amounts of vitamin E, for example, can sometimes push the supply of the nutrient high enough to cause mild toxicity. Supplementing 3000 IU/day of vitamin E to transition cows with adequate vitamin E status resulted in pro-oxidant responses, increasing markers of lipid peroxidation and the incidence of mastitis (Bouwstra et al., 2010). Any treatment that alters oxidative balance should be evaluated carefully.

Finally, non-nutritive antioxidants may also serve to limit oxidative stress. In one recent study, supplementation of a feed antioxidant decreased peroxide and tended to increase total antioxidant capacity in plasma when fed to cows in early lactation (Wang et al., 2010). These responses were observed despite the presumed lack of absorption of these antioxidants, suggesting that simply limiting the absorption of unstable oxidized lipids from the diet can help to control oxidative stress. Such an approach would presumably also avoid any risk of toxicity from feeding high amounts of lipid-soluble vitamins.

Other nutritional approaches

In light of the documented links between metabolites associated with negative energy balance (NEFA, BHBA, and ROS), nutritional strategies already in place to minimize the incidence of "fat cow syndrome" should also promote immune function. Therefore, typical recommendations for dry cow nutrition deserve continued attention.

A more recent and novel approach evaluated by Thatcher and colleagues (Silvestre et al., 2011a) was to promote immune function in the transition period by supplementing omega-6 FA, supplied in the form of calcium salts of FA. Although this form of FA protection does not make the FA inert in the rumen, biohydrogenation is slowed enough for these supplements to alter FA composition of tissues. Increasing the ratio of omega-6 to omega-3 FA (as well as total *trans*-FA) increased the production of hydrogen peroxide and phagocytosis of bacteria by neutrophils (Silvestre et al., 2011a). This treatment also increased plasma concentrations of 2 acute phase proteins, indicating a more inflamed state of the liver during the transition period. Although liver inflammation is associated with impaired metabolic function (Bertoni et al., 2008; Bradford et al., 2009), no effects on plasma BHBA or glucose were detected in this study (Silvestre et al., 2011b). The use of a relatively pro-inflammatory lipid source early postpartum, followed by an omega-3 enriched diet during breeding (Silvestre et al., 2011a), is a strategy that deserves further investigation to determine if it can consistently enhance immune function without negatively impacting metabolic function.

Conclusions

The demonstrated links between the immune and metabolic systems of the dairy cow highlight the importance of viewing health problems in transition cows from a holistic perspective. Nutritional strategies aimed at improving metabolic function, delivering bioactive nutrients, and supporting antioxidant systems in the cow can help to prevent a vicious cycle that can sustain both subclinical infections and metabolic dysfunction.

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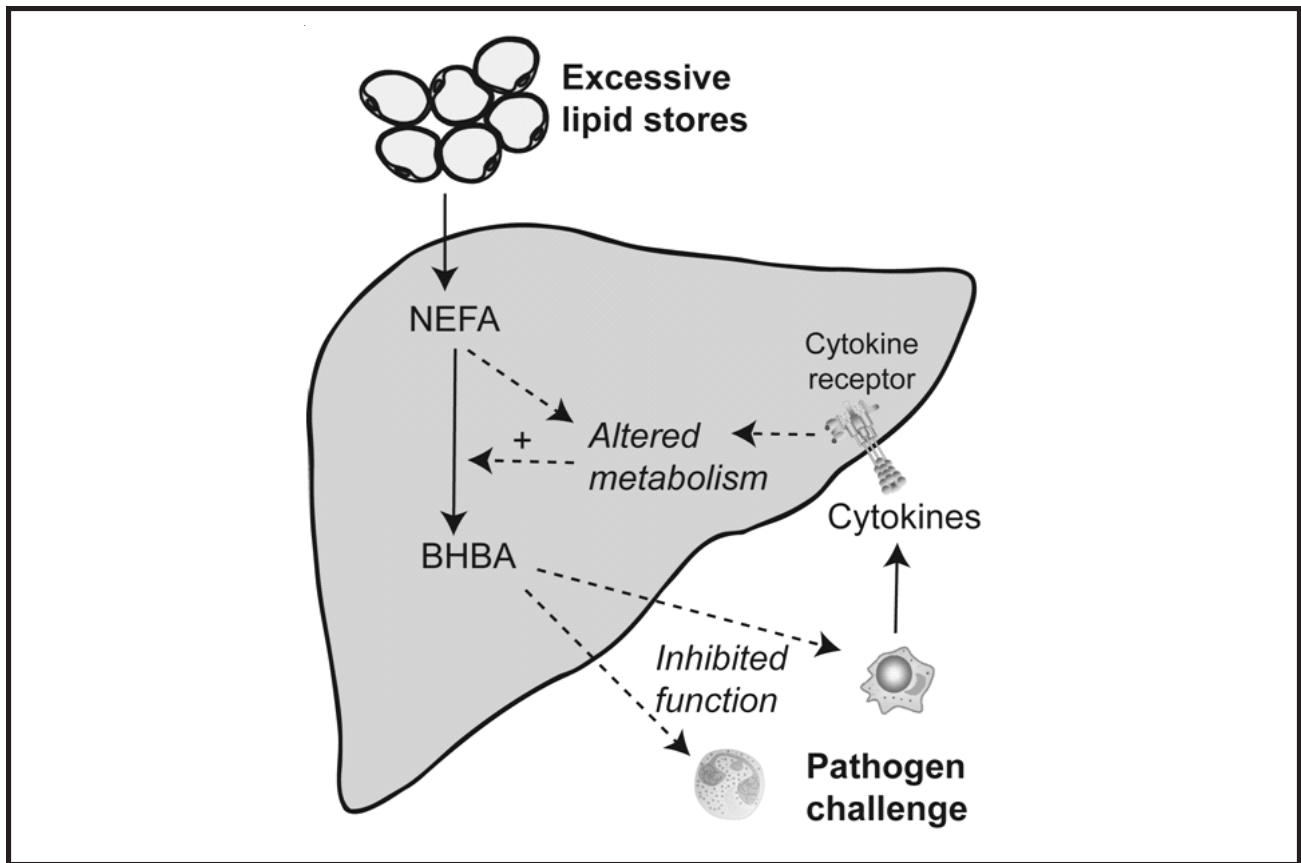
Figure 1. Cross-talk between immune and metabolic systems can promote a positive feedback loop promoting disease complexes. Excessive lipid storage in adipose tissue and pathogen challenges (activating neutrophils and macrophages, bottom right) are known risk factors for both metabolic and infectious disorders in transition cows. Cytokine signals from immune activation, along with inflammatory effects of excessive intracellular lipids in the liver, contribute to alterations in metabolism, including enhanced ketogenesis. Ketones released by the liver, in turn, suppress the function of immune cells, which can result in delayed clearance of pathogens and sustained inflammation. This positive feedback can sustain a combined metabolic and infectious disease problem that can spiral out of control if not interrupted.