HEAT STRESS: WHAT'S THE GUT GOT TO DO WITH IT?

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TAKE HOME MESSAGE

Heat stress (HS) is a global problem which jeopardizes animal welfare, profitability, and global food security. Indirect effects of HS such as reduced feed intake contribute to, but do not fully explain, decreased productivity. Heat stressed animals initiate metabolic changes that do not reflect their plane of nutrition. This indicates that HS directly effects metabolism and productivity independent of reduced feed intake. In a variety of species, environmental hyperthermia compromises the intestinal barrier function resulting in increased permeability to luminal content including bacteria and bacterial components. Presumably, heat stress causes leaky gut in ruminants as well. The leakage of luminal content into the portal and ultimately the systemic circulation elicits an inflammatory response that may facilitate the detrimental effects of HS on animal agriculture. Identifying flexible management strategies (i.e. nutritional supplementation) to immediately decrease HS susceptibility without negatively influencing production traits would be of great value to global animal agriculture.

INTRODUCTION

Economic Impact

Heat stress negatively impacts a variety of dairy production parameters including milk yield, milk quality and composition, rumen health, growth and reproduction, and is a significant financial burden (~$900 million/year for dairy, and > $300 million/year in beef and swine in the U.S. alone; St. Pierre et al., 2003; Pollman, 2010). When the ambient temperature and other environmental conditions create a situation that is either below or above the respective threshold values, efficiency is compromised because nutrients are diverted to maintain euthermia as preserving a safe body temperature becomes the highest priority, and product synthesis (milk, meat, etc.) is deemphasized. Advances in management (i.e. cooling systems; VanBaale et al., 2005) and nutritional strategies (West, 2003) have partially alleviated the negative impacts of HS on cattle, but productivity continues to decline during the summer. The detrimental effects of HS on animal welfare and production will likely become more of an issue in the future if the earth's climate continues to warm as predicted (IPCC 2007) and some models forecast extreme summer conditions in most U.S. animal producing areas (Luber and McGeehin, 2008). A 2006 California heat wave purportedly resulted in the death of more than 30,000 dairy cows (CDFA, 2006) and a recent heat wave in Iowa killed at least 4,000 head of beef cattle (Drovers Cattle Network, 2011). Furthermore, almost 50% of

Canadian summer days are environmentally stressful to dairy cows (Ominski et al., 2002). This illustrates that most geographical locales, including temperate and northern climates, are susceptible to extreme and lethal heat. Thus, for a variety of aforementioned reasons, there is an urgent need to have a better understanding of how HS alters nutrient utilization and ultimately reduces animal productivity. Defining the biology of how HS jeopardizes animal performance is critical in developing approaches (genetic, managerial, nutritional and pharmaceutical) to ameliorate current production issues and improve animal well-being and performance. This would help secure the global agricultural economy by ensuring a constant supply of animal products for human consumption.

Direct and Indirect Effects of Heat Stress

Reduced feed intake during HS is a highly conserved response among species and presumably represents an attempt to decrease metabolic heat production (Baumgard and Rhoads, 2012). It has traditionally been assumed that inadequate feed intake caused by the thermal load was responsible for decreased milk production (Beede and Collier, 1986; West, 2003). However, our recent results challenge this dogma as we have demonstrated disparate slopes in feed intake and milk yield responses to a cyclical heat load pattern (Shwartz et al., 2009). To test this, we employed the use of a thermoneutral pair-fed group in our experiments which allowed us to evaluate thermal stress while eliminating the confounding effects of dissimilar nutrient intake. Our experiments demonstrate that reduced feed intake only explains approximately 35-50% of the decreased milk yield during environmental-induced hyperthermia (Rhoads et al., 2009a; Wheelock et al., 2010; Baumgard et al., 2011). This indicates that HS directly effects nutrient partitioning beyond that expected by reduced feed intake.

An appreciation of the physiological and metabolic adjustments to thermoneutral negative energy balance (NEBAL; i.e. underfeeding or during the transition period) is prerequisite to understanding metabolic adaptations occurring with HS. Early lactation dairy cattle enter a unique physiological state during which they are unable to consume enough nutrients to meet maintenance and milk production costs and typically enter NEBAL (Baumgard and Rhoads, 2013). Negative energy balance is associated with a variety of metabolic changes that are implemented to support the dominant physiological condition of lactation (Bauman and Currie, 1980). Marked alterations in both carbohydrate and lipid metabolism ensure partitioning of dietary and tissue derived nutrients towards the mammary gland, and not surprisingly many of these changes are mediated by endogenous somatotropin which naturally increases during periods of NEBAL. One classic response is a reduction in circulating insulin coupled with a reduction in systemic insulin sensitivity. The reduction in insulin action activates adipose lipolysis, leading to the mobilization of non-esterified fatty acids (NEFA; Bauman and Currie, 1980). Increased circulating NEFA are typical in transitioning cows and represent (along with NEFA derived ketones) a significant source of energy (and precursors for milk fat synthesis) for cows in NEBAL. Postabsorptive carbohydrate metabolism is also altered by reduced insulin action during NEBAL resulting in reduced

glucose uptake by systemic tissues (i.e. muscle and adipose). Reduced nutrient uptake coupled with the net release of nutrients (i.e. amino acids and NEFA) by systemic tissues are key homeorhetic (an acclimated response vs. an acute/homeostatic response) mechanisms implemented by cows in NEBAL to support lactation. The thermoneutral cow in NEBAL is metabolically flexible, and can depend upon alternative fuels (NEFA and ketones) to spare glucose. Glucose can then be utilized by the mammary gland to copiously produce milk (Bauman and Currie, 1980).

Well-fed ruminants primarily oxidize acetate (a rumen produced VFA) as a principal energy source. During NEBAL, cattle increase their energy dependency on NEFA. However, despite the fact that heat stressed cows have marked reductions in feed intake and are losing considerable amounts of body weight, they do not mobilize adipose tissue (Rhoads et al., 2009a; Wheelock et al., 2010). Therefore, it appears that heat stressed cattle experience altered post-absorptive metabolism compared to thermoneutral counterparts, even though they are in a similar negative energetic state (Moore et al., 2005; Rhoads et al., 2013). The unusual lack of NEFA response in heat stressed cows is probably in part explained by increased circulating insulin levels (O'Brien et al., 2010; Wheelock et al., 2010), as insulin is a potent anti-lipolytic hormone. Increased circulating insulin during HS is unusual as malnourished animals are in a catabolic state and experience decreased insulin levels. We have recently demonstrated that heat stressed growing pigs undergo similar metabolic adaptations (Pearce et al., 2013a), suggesting that this is a well conserved response vital for the acclimation to HS. Increased insulin action may also explain why heat stressed animals have greater rates of glucose disposal (Wheelock et al., 2010). Therefore, during HS, preventing or blocking adipose mobilization/breakdown and increasing glucose "burning" is presumably a strategy to minimize metabolic heat production (Baumgard and Rhoads, 2013). The enhanced extra-mammary glucose utilization during HS creates a nutrient trafficking problem with regards to milk yield. The mammary gland requires glucose to synthesize milk lactose which is the primary osmoregulator determining overall milk volume. Therefore, the mammary gland may not receive adequate amounts of glucose resulting in reduced mammary lactose and subsequent milk production. This may be a primary mechanism accounting for additional reductions in milk yield beyond the portion explained by decreased feed intake.

LEAKY GUT: RESPONSIBLE FOR THE DIRECT EFFECTS OF HEAT STRESS?

Mechanisms responsible for altered nutrient partitioning during HS are not clear, however, they might be mediated by HS effects on gastrointestinal health and function (Figure 1). The small intestine is one of the first tissues up-regulating heat shock proteins during a thermal load (Flanagan et al., 1995), demonstrating a higher sensitive to heat damage (Kregel, 2002). During heat stress, blood flow is diverted from the viscera to the periphery in an attempt to dissipate heat (Lambert et al., 2002), leading to intestinal hypoxia (Hall et al., 1999). Enterocytes are particularly sensitive to hypoxia and nutrient restriction (Rollwagen et al., 2006), resulting in ATP depletion and increased oxidative and nitrosative stress (Hall et al., 2001). This contributes to tight

junction dysfunction, and gross morphological changes that ultimately reduce intestinal barrier function (Lambert et al., 2002; Pearce et al., 2013b). As a result, HS increases the passage of luminal content as lipopolysaccharide (LPS) into the portal and systemic blood (Hall et al., 2001; Pearce et al., 2013b). Further, endotoxemia is common among heat stroke patients (Leon, 2007) and it is thought to play a central role in heat stroke pathophysiology, as survival increases when intestinal bacterial load is reduced (Bynum et al., 1979) or when plasma LPS is neutralized (Gathiram et al., 1987). It is remarkable how animals suffering from heat stroke or severe endotoxemia share many physiological and metabolic similarities such as an increase in circulating insulin (Lim et al., 2007). Infusing LPS into the mammary gland increased (~2 fold) circulating insulin in lactating cows (Waldron et al., 2006). In addition, we intravenously infused LPS into growing calves and pigs and demonstrated >10 fold increase in circulating insulin (Rhoads et al., 2009b; Stoakes and Baumgard, unpublished). Again, the increase in insulin in both models is energetically difficult to explain as feed intake was severely depressed in both experiments.

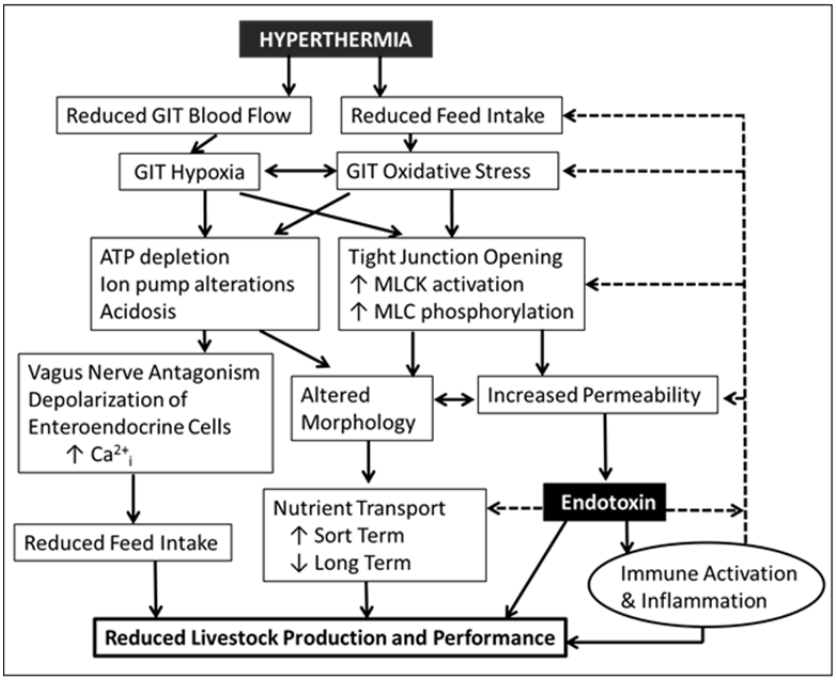

Figure 1: Etiology of heat stress induced leaky gut

Intestinal Integrity & Steatohepatitis

Interestingly, a variety of diseases associated with increased intestinal permeability such as heat stress and stroke, Crohn's disease, inflammatory bowel disease, Celiac disease, and alcoholism are often associated with increased plasma LPS concentrations and an inflammatory acute phase response (Bouchama et al., 1993; Pearce, et al. 2013b; Draper et al., 1983; Parlesak et al., 2000; Ludvigsson et al., 2007). There is increasing evidence that translocation of gut microbiota contributes to hepatic inflammation (Bieghs and Trautwein, 2013) which might impair liver function leading to fat accumulation and ultimately steatohepatitis (Ilan, 2012; Dumas et al.,

2006; Solga and Diehl, 2003; Farhadi et al., 2008; Miele et al., 2009). The association between leaky gut and fatty liver is of particular interest in the ruminant animal who is already an inefficient exporter of hepatic lipids. There is reason to believe that similar breakdown of gut integrity may be responsible for hepatic disorders (e.g. fatty liver and ketosis; Figure 2) frequently observed in the transition dairy cow. A transitioning dairy cow undergoes a post-calving diet shift from a mainly forage based to a high concentrate ration. This has the potential to induce rumen acidosis which can compromise the gastrointestinal tract barrier (Khafipour et al., 2009). In addition, calving is a physically stressful event and cytokines released from the damaged reproductive tract may have an impact on the liver's ability to export lipids. Preliminary data has shown an increase in plasma lipopolysaccharide binding protein (LPSBP), an acute phase protein which binds LPS to stimulate an immune response, in cows that required treatment for clinical ketosis compared to healthy transition cows (Nayeri et al., 2012). Nevertheless, the effects of the transition period on the intestinal barrier function and its role in the development of fatty liver and ketosis among other transition disorders remain unknown and require further investigation.

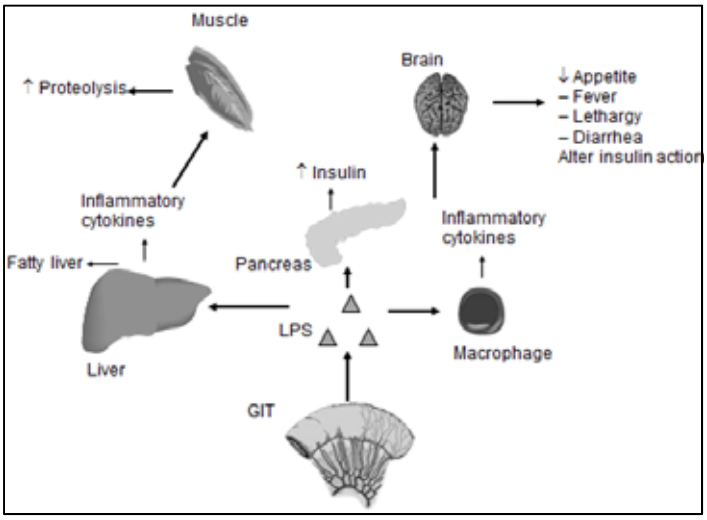

Figure 2: LPS induced metabolic alterations

NUTRITIONAL STRATEGIES TO PREVENT LEAKY GUT

Bicarbonate

Acidosis may exacerbate intestinal issues (Khafipour et al., 2009) as rumen pH is lowered during the summer months (Mishera et al., 1970). This may be explained by increased respiration rate which decreases blood carbon dioxide (CO_2) and increases the need for the kidney to secrete bicarbonate to maintain a healthy 20 to 1 ratio of bicarbonate to CO_2 in the blood. Increased secretion of bicarbonate by the kidney reduces the amount available to be used in the saliva to buffer rumen pH. In addition, reduced feed intake results in reduced rumination time which is a key stimulator of saliva production. Thus, the increased susceptibility of heat-stressed cattle to rumen acidosis might be prevented by dietary bicarbonate supplementation.

Glutamine

Glutamine is a conditionally non-essential amino acid as it can be formed from ammonia and and glutamate. It is a primary energy source for intestinal cells (Singleton and Wischmeyer, 2006) and supplemental dietary glutamine has demonstrated improvement in intestinal barrier function in malnourished children (Lima et al., 2005). A potential mechanism of action for glutamine's beneficial effects is the enhanced expression of heat-shock protein 70 (Singleton and Wichmeyer, 2006). Glutamine supplementation to high producing thermoneutral cows did not improve milk yield (Metcalf et al., 1996). However, a study by Caroprese and co-workers (2013) demonstrated that during HS, glutamine supplementation improved milk, fat, protein, and casein yields. Caroprese and colleagues also observed improvement in cell mediated immune response which was likely responsible for the observed lower somatic cell count, possibly indicating a role for glutamine in the alleviation of mastitis.

Zinc

Dietary zinc is essential for normal intestinal barrier function (Alam et al., 1994), and supplemental zinc is beneficial in a variety of animal models and human diseases characterized by increased intestinal permeability (Alam et al., 1994; Zhang and Guo, 2009). We have recently demonstrated that supplemental zinc can partially alleviate the effects HS on intestinal integrity in acute and chronically heat-stressed growing pigs (Sanz-Fernandez et al., 2014; Pearce et al., 2013b). The mechanisms by which zinc improves intestinal integrity are not well understood, but might include: the up-regulation of tight junction proteins (Zhang and Guo, 2009), a role as antioxidant via induction of metallothioneins (Wang et al., 2013), and/or increasing the expression of antimicrobial substances as β-defensins (Mao et al., 2013).

Dairy Products

Dietary dairy products (e.g. colostrum and whey protein) have been also demonstrated to improve intestinal health under different types of challenges (Playford et al., 1999 and 2001; Khan et al., 2002; Prosser et al., 2004). Interestingly, dietary dairy products have demonstrated alleviation of HS effects on the intestinal barrier function both *in vivo* (Prosser et al., 2004) and *in vitro* (Marchbank et al., 2011). Once again their mechanisms of action are not well understood but both colostrum and whey protein are rich in antimicrobial proteins (e.g. glucomacropeptides, lactoferrin), immunoglobulins, growth factors (e.g. Transforming Growth Factor-β), and certain amino acids (glutamine, cysteine, and threonine; Krissansen, 2007). Further, dietary dairy products have shown to up-regulation heat-shock protein 70 (Marchbank et al., 2011) and tight junction proteins (mediated by TGF-β; Hering et al., 2011), and increase mucin production (mediated by threonine and cysteine; Sprong et al., 2010); which might explain their beneficial effect on intestinal health.

Inhibiting milk fat synthesis during HS may attenuate or eliminate the negative energy balance. As a result of the extra available energy, synthesis of other milk and milk components may increase (i.e., lactose and protein). In addition to enhancing milk yield, inhibiting milk fat synthesis and thus improving energy balance may improve animal well-being and reproductive success (Bauman et al., 2001). We utilized conjugated linoleic acid (CLA) in an attempt to strategically improve energy balance during HS, but did not detect any noticeable improvement in production variables (Moore et al., 2005).

Antioxidants

Hypoxia of the small intestine during HS can lead to oxidative stress and production of free radicals (Hall et al., 1999). In addition, intestinal inflammation leads to loss of antioxidant capacity (Buffinton and Doe, 1995b). Therefore, supplementation of antioxidants such as selenium and vitamins A, E, and C during HS is of great interest.

Vitamin A can mitigate the effects of induced mucosal damage (Elli et al., 2009) and deficiency can have negative effects on immunity and integrity in the gut (Yang et al., 2011; Thurnham et al., 2000). This was the case of vitamin A-deficient beef calves that suffered reduced intestinal integrity and were more susceptible to a secondary E. coli infection (He, et al., 2012). Dietary vitamin A has the potential to improve weight gain and feed efficiency in HS broilers and this effect was amplified when vitamin A was combined with zinc (Kucuk et al., 2003). In addition, cows supplemented with β-carotene during hot months had increased milk yield and pregnancy rates (Aréchiga et al., 1998).

Table 1. Potential nutritional strategies to ameliorate intestinal permeability

Supplement	Presumed Mechanism of Action
Bicarbonate	Acidosis prevention
Glutamine	↑ intestine integrity
Zinc	↑ intestine integrity
Dairy Products	↑ intestine integrity
Vitamin A	Antioxidant
Vitamin C	Antioxidant
Vitamin E	Antioxidant
Selenium	Antioxidant
Dexamethasone	↑ intestine integrity
Betaine	Osmotic regulation; CH_3 donor
Conjugated Linoleic Acid	↑ Energy balance

Vitamin E supplementation has reduced gut bacterial translocation and increased survival in radiation induced intestinal injury (Singh et al., 2012). Supplementation also increases vitamin A serum concentrations, suggesting a protective role for vitamin E on vitamin status (Sahin et al., 2002b). Sahin and coworkers (2002a) also demonstrated improved production performance in Japanese quails supplemented with vitamin C and

E during HS. Dairy cows administered 3000 IU of vitamin E during two consecutive summers had similar pregnancy rates compared to controls (Ealy et al., 1994), however little research has examined its effects on production and immune status in dairy cows.

Vitamin C is decreased in inflammatory bowel disease patients (Buffinton and Doe, 1995a) as well as heat stressed lactating cows (Padilla and Matsuia, 2006). Supplementation has demonstrated positive effects during HS by reducing tocopheroxyl radicals back to the active form of vitamin E (Sahin, 2002b).

Selenium is part of selenoproteins such as glutathione peroxidase, which is a major free radical scavenger system in the cell (Loeb et al., 1988). Selenoproteins also play an important role in cell growth as deficiency has been linked to DNA damage and poor cell cycle control (Rao et al., 2001) which may be pertinent to intestinal integrity due to high enterocyte turnover rate. In patients with celiac disease, characterized by small intestine damage, selenium deficiency is a risk factor due to poor absorption which can lead to increased reactive oxygen species and inflammation (Stazi and Trinti, 2008; Barrett et al., 2013). Supplementation with selenium has the potential to reduce lipid peroxidation and epithelial damage to intestinal mucosa, and prevent bacterial translocation (Baldwin and Wiley, 2002; Oztürk et al., 2002). Sheep injected with selenium during HS lost less weight compared to their HS control counterparts (Alhidary et al., 2012).

Many of the antioxidant compounds listed above have synergistic effects with one another or with minerals like zinc (Kucuk et al., 2003; Sahin et al., 2002a, 2002b). Research demonstrating effects of supplemental antioxidant on production parameters during HS is scarce and further research is needed to allow for the development of supplementation recommendations, particularly in ruminants.

Dexamethasone

Dexamethasone is a synthetic corticosteroid with anti-endotoxic and anti-inflammatory properties. Previous research has demonstrated a marked increase in corticosteroids in response to HS (Collier et al., 1982; Baumgard and Rhoads, 2013). Dexamethasone prevented the increase in plasma aspartate transaminase and alanine aminotransferase (both markers of hepatic health), IL-6 and LPS in a rat model of heat stroke, probably by blocking endotoxemia (Lim et al., 2007). Also in a heat stroke model, primates injected with corticosteroid had reduced endotoxemia as well as an increased survival rate (Gathiram et al., 1988a, 1988b). Further research is needed within the livestock industry to explore potential pharmacological roles of dexamethasone in heat stress abatement practices.

Betaine

Betaine, also known as trimethylglycine, is an osmotic regulator and methyl donor which may exhibit several beneficial effects in heat-stressed animals including the potential to protect against osmotic stress by decreasing sodium potassium pump activity (Cronje, 2007).

Betain supplementation improves intestinal integrity in both healthy and coccidian infected birds (Kettunen et al., 2001). In addition, betaine ameliorated the effects of HS on weight gain, immunity and body temperature indices in rabbits (Hassan et al., 2011). Supplemented thermoneutral mid-lactation dairy cows experienced an increase in milk yield, a decrease in milk protein percent, and altered milk fatty acid profile (Peterson et al., 2012). However, no differences were observed in milk production parameters in HS cows (Hall et al., 2012). Lack of sufficient evidence in support of or against betaine's role in HS alleviation warrants the need for further investigation.

MANAGEMENT STRATEGIES

Despite increased efforts to combat HS through nutritional strategies, cooling technology and management practices still represent the main approach to relieve HS. Providing shade, ventilation, and cooling as well as reducing walking distance can be strategies implemented to reduce the harmful effects of HS. Increasing milking frequency is strategy that has not been thoroughly evaluated during HS, but is a well-described lactogenic stimulant during thermal neutral conditions (Fitzgerald et al., 2007). Controlling the timing of feeding is also beneficial, as early morning and late night feeding helps to push the peak heat of fermentation to cooler parts of the day. Pushing up feed often so cows consume several small meals instead of a few large meals will aid in acidosis prevention and reduce steep increases in metabolic heat caused by consuming a large meal. Stressors of any kind (i.e. vaccinations) should be avoided during hotter parts of the day as the combination of HS and handling stress is unfavorable. Administration of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may exacerbate gastrointestinal integrity issues.

CONCLUSION

High ambient temperatures have a negative effect on animal health and performance, costing billions of dollars in losses to global animal agriculture. Gut integrity is compromised by HS and the resultant systemic inflammation might partially explain its negative effects on production. Nutrition is an example of an easily adjustable tactic to ameliorate the detrimental effects of environmental hyperthermia. For instance, heat-stressed animals shift energy metabolism toward carbohydrate usage and reduce lipid oxidation. Therefore, diets or nutritional supplements promoting glucose production (i.e. ionophores) and utilization may be useful. In addition, intestinal health improvement via dietary supplementation might be advantageous. Finally, cooling management practices such as shade, evaporative cooling, and strategic timing of farm activities aid in the mitigation of the adverse effects of HS. Even in today's most

well managed dairies, HS remains a problem. In order to resolve current HS production issues and develop better mitigation strategies, a better understanding of the biology and mechanisms of how HS threatens animal health is essential.

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WORK CITED

Alam, A.N., S.A. Sarker, M.A. Wahed, M. Khatun, and M.M. Rahaman. 1994. Enteric protein loss and intestinal permeability changes in children during acute shigellosis and after recovery: effect of zinc supplementation. Gut 35,1707-1711.

Alhidary, I. A., S. Shini, R. A. Al Jassim, and J. B. Gaughan. 2012. Effect of various doses of injected selenium on performance and physiological responses of sheep to heat load. J Anim Sci 90: 2988-2994.

Aréchiga, C. F., C. R. Staples, L. R. McDowell, and P. J. Hansen. 1998. Effects of timed insemination and supplemental beta-carotene on reproduction and milk yield of dairy cows under heat stress. J Dairy Sci 81: 390-402.

Baldwin, A. L., and E. B. Wiley. 2002. Selenium reduces hemoglobin-induced epithelial damage to intestinal mucosa. Artif Cells Blood Substit Immobil Biotechnol 30: 1-22.

Barrett, C. W. Singh, K., Motley, A. K., Lintel, M. K., Matafonova, E., Bradley, A. M., Ning, W., Poindexter, S. V., Parang, B., Reddy, V. K., Chaturvedi, R., Fingleton, B. M., Washington, M. K., Wilson, K. T., Davies, S. S., Hill, K. E., Burk, R. F. & Williams, C. S. 2013. Dietary Selenium Deficiency Exacerbates DSS-Induced Epithelial Injury and AOM/DSS-Induced Tumorigenesis. PLoS One 8: e67845.

Bauman, D. E., and W. B. Currie. 1980. Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis. J Dairy Sci 63: 1514-1529.

Bauman, D.E., D.G. Peterson, B.A. Corl, L.H. Baumgard and J. W. Perfield II. 2001. Update on conjugated linoleic acids (CLA). Proc. Cornell Nutr. Conf. pp 170-178.

Baumgard, L., and R. Rhoads. 2013. Effects of heat stress on postabsorptive metabolism and energetics. Annual Review of Animal Biosciences 1: 7.1-7.27.

Baumgard, L., Rhoads, R., Rhoads, M., Gabler, N., Ross, J., Keating, A., Boddicker, R., Lenka, S. & Sejian, V. 2012. Impact of climate change on livestock production. In: V. Sejian, S. Nagvi, T. Ezeji, J. Lakritz and R. Lal (eds.) Impact of climate change on livestock production. Chapter 15. Environmental Stress and Amelioration in Livestock Production. Springer.

Baumgard, L. H., and R. P. Rhoads. 2012. Ruminant Nutrition Symposium: ruminant production and metabolic responses to heat stress. J Anim Sci 90: 1855-1865.

Baumgard, L. H., Wheelock, J. B., Sanders, S. R., Moore, C. E., Green, H. B., Waldron, M. R. & Rhoads, R. P. 2011. Postabsorptive carbohydrate adaptations to heat stress and monensin supplementation in lactating Holstein cows. J Dairy Sci 94: 5620-5633.

Beede, D., and R. Collier. 1986. Potential nutritional strategies for intensively managed cattle during thermal stress. Journal of Animal Science 62: 543-554.

Begriche, K., A. Igoudjil, D. Pessayre, and B. Fromenty. 2006. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion 6: 1-28.
Bieghs, V., and C. Trautwein. 2013. The innate immune response during liver inflammation and metabolic disease. Trends Immunol.
Bouchama, A., S. al-Sedairy, S. Siddiqui, E. Shail, and M. Rezeig. 1993. Elevated pyrogenic cytokines in heatstroke. Chest 104: 1498-1502.
Buffinton, G. D., and W. F. Doe. 1995a. Altered ascorbic acid status in the mucosa from inflammatory bowel disease patients. Free Radic Res 22: 131-143.
Buffinton, G. D., and W. F. Doe. 1995b. Depleted mucosal antioxidant defences in inflammatory bowel disease. Free Radic Biol Med 19: 911-918.
Bynum, G., J. Brown, D. Dubose, M. Marsili, I. Leav, T.G. Pistole, M. Hamlet, M. LeMaire, and B. Caleb. 1979. Increased survival in experimental dog heatstroke after reduction of gut flora. Aviat Space Environ Med 50, 816-819.
Caroprese, M., M. Albenzio, R. Marino, A. Santillo, and A. Sevi. 2013. Dietary glutamine enhances immune responses of dairy cows under high ambient temperature. J Dairy Sci 96: 3002-3011.
CDFA. 2008. Hot topics affecting California Agriculture. An update from Sec. Kawamura. California Department of Food Agriculture.
Chan, S. C., J. T. Huber, K. H. Chen, J. M. Simas, and Z. Wu. 1997. Effects of ruminally inert fat and evaporative cooling on dairy cows in hot environmental temperatures. J Dairy Sci 80: 1172-1178.
Chandler, P. 1994. Is heat increment of feeds an asset or liability to milk production? Feedstuffs No. 66.
Chapinal, N., Carson, M., Duffield, T. F., Capel, M., Godden, S., Overton, M., Santos, J. E. & LeBlanc, S. J. 2011. The association of serum metabolites with clinical disease during the transition period. J Dairy Sci 94: 4897-4903.
Collier RJ, Beede DK, Thatcher WW, Israel LA, Wilcox CJ.1982. Influences of environment and its modification on dairy animal health and production. J Dairy Sci 65:2213-27.
Cronje, P. 2005. Heat stress in livestock—the role of the gut in its aetiology and a potential role for betaine in its alleviation. Recent Advances in Animal Nutrition in Australia 15: 107-122.
Drackley, J. K. 1999. ADSA Foundation Scholar Award. Biology of dairy cows during the transition period: the final frontier? J Dairy Sci 82: 2259-2273.
Drackley, J. K., T. M. Cicela, and D. W. LaCount. 2003. Responses of primiparous and multiparous Holstein cows to additional energy from fat or concentrate during summer. J Dairy Sci 86: 1306-1314.
Draper, L. R., L. A. Gyure, J. G. Hall, and D. Robertson. 1983. Effect of alcohol on the integrity of the intestinal epithelium. Gut 24: 399-404.
Drovers Cattle Network. 2011. Heat wave kills as many as 4,000 cattle last week in Iowa. http://www.cattlenetwork.com/cattle-resources/hot-topics/Heat-wave-kills-as-many-as-4000-cattle-last-week-in-Iowa-126763608.html
Duffield, T. F., K. D. Lissemore, B. W. McBride, and K. E. Leslie. 2009. Impact of hyperketonemia in early lactation dairy cows on health and production. J Dairy Sci 92: 571-580.

Dumas, M. E., Barton, R. H., Toye, A., Cloarec, O., Blancher, C., Rothwell, A., Fearnside, J., Tatoud, R., Blanc, V., Lindon, J. C., Mitchell, S. C., Holmes, E., McCarthy, M. I., Scott, J., Gauguier, D. & Nicholson, J. K. 2006. Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. Proc Natl Acad Sci U S A 103: 12511-12516.

Ealy, A. D., C. F. Aréchiga, D. R. Bray, C. A. Risco, and P. J. Hansen. 1994. Effectiveness of short-term cooling and vitamin E for alleviation of infertility induced by heat stress in dairy cows. J Dairy Sci 77: 3601-3607.

Elli, M., Aydin, O., Bilge, S., Bozkurt, A., Dagdemir, A., Pinarli, F. G. & Acar, S. 2009. Protective effect of vitamin A on ARA-C induced intestinal damage in mice. Tumori 95: 87-90.

Farhadi, A, Gundlapalli, S., Shaikh, M., Frantzides, C., Harrell, L., Kwasny, M. M. & Keshavarzian, A. 2008. Susceptibility to gut leakiness: a possible mechanism for endotoxaemia in non-alcoholic steatohepatitis. Liver Int 28: 1026-1033.

Fitzgerald, A.C., E.L. Annen-Dawson, L.H. Baumgard, and R.J. Collier. 2007. Evaluation of continuous lactation, and increased milking frequency on milk production and mammary cell turnover in primiparous Holstein cows. J. Dairy Sci. 90:5483-5489.

Flanagan, S.W., A.J. Ryan, C.V. Gisolfi, and P.L. Moseley. 1995. Tissue-specific HSP70 response in animals undergoing heat stress. Am J Physiol 268, R28-32.

Gathiram, P., M.T. Wells, J.G. Brock-Utne, and S.L. Gaffin. 1987. Antilipopolysaccharide improves survival in primates subjected to heat stroke. Circ Shock 23,157-164.

Gathiram, P., S. L. Gaffin, J. G. Brock-Utne, and M. T. Wells. 1988a. Prophylactic corticosteroid suppresses endotoxemia in heat-stressed primates. Aviat Space Environ Med 59: 142-145.

Gathiram, P., M. T. Wells, J. G. Brock-Utne, and S. L. Gaffin. 1988b. Prophylactic corticosteroid increases survival in experimental heat stroke in primates. Aviat Space Environ Med 59: 352-355.

Geishauser, T., K. Leslie, J. Tenhag, and A. Bashiri. 2000. Evaluation of eight cow-side ketone tests in milk for detection of subclinical ketosis in dairy cows. J Dairy Sci 83: 296-299.

Gillund, P., O. Reksen, Y. T. Gröhn, and K. Karlberg. 2001. Body condition related to ketosis and reproductive performance in Norwegian dairy cows. J Dairy Sci 84: 1390-1396.

Hall, D. M., K. R. Baumgardner, T. D. Oberley, and C. V. Gisolfi. 1999. Splanchnic tissues undergo hypoxic stress during whole body hyperthermia. Am J Physiol 276: G1195-1203.

Hall, D.M., G.R. Buettner, L.W. Oberley, L. Xu, R.D. Matthes, and C.V. Gisolfi. 2001. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. Am J Physiol Heart Circ Physiol 280, H509-521.

Hall, L., Dunshea, F., Allen, J., Wood, A., Anderson, S., Rungruang, S., Collier, J., Long, N. & Collier, R. 2012. Evaluation of dietary betaine (BET) in heat-stressed Holstein cows in lactation Ruminant Nutrition: Dairy: Feed Additives. J Anim Sci 90 E-Suppl. 3:556.

Hassan, R., T. Ebeid, A. Abd El-Lateif, and N. Ismail. 2011. Effect of dietary betaine supplementation on growth, carcass and immunity of New Zealand White rabbits under high ambient temperature. Livestock Science 135: 103-109.
He, X., Li, Y., Li, M., Jia, G., Dong, H., Zhang, Y., He, C., Wang, C., Deng, L. & Yang, Y. 2012. Hypovitaminosis A coupled to secondary bacterial infection in beef cattle. BMC Vet Res 8: 222.
Hering, N. A. et al. 2011. Transforming growth factor-β, a whey protein component, strengthens the intestinal barrier by upregulating claudin-4 in HT-29/B6 cells. J Nutr 141: 783-789.
Huzzey, J. M., D. V. Nydam, R. J. Grant, and T. R. Overton. 2011. Associations of prepartum plasma cortisol, haptoglobin, fecal cortisol metabolites, and nonesterified fatty acids with postpartum health status in Holstein dairy cows. J Dairy Sci 94: 5878-5889.
Ilan, Y. 2012. Leaky gut and the liver: a role for bacterial translocation in nonalcoholic steatohepatitis. World J Gastroenterol 18: 2609-2618.
IPCC. 2007. IPCC WGI Fourth Assessment Report. Climatic Change: the physical science basis, Geneva.
Kettunen, H., K. Tiihonen, S. Peuranen, M. T. Saarinen, and J. C. Remus. 2001. Dietary betaine accumulates in the liver and intestinal tissue and stabilizes the intestinal epithelial structure in healthy and coccidia-infected broiler chicks. Comp Biochem Physiol A Mol Integr Physiol 130: 759-769.
Khafipour, E., D. O. Krause, and J. C. Plaizier. 2009. A grain-based subacute ruminal acidosis challenge causes translocation of lipopolysaccharide and triggers inflammation. J Dairy Sci 92: 1060-1070.
Khan, Z., C. Macdonald, A.C. Wicks, M.P. Holt, D. Floyd, S. Ghosh, N.A. Wright, and R.J. Playford. 2002. Use of the 'nutriceutical', bovine colostrum, for the treatment of distal colitis: results from an initial study. Aliment Pharmacol Ther 16, 1917-1922.
Knapp, D. M., and R. R. Grummer. 1991. Response of lactating dairy cows to fat supplementation during heat stress. J Dairy Sci 74: 2573-2579.
Kregel, K.C. 2002. Heat shock proteins: modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol 92, 2177-2186.
Krissansen, G.W. 2007. Emerging health properties of whey proteins and their clinical implications. J Am Coll Nutr 26, 713S-723S.
Kucuk, O., N. Sahin, and K. Sahin. 2003. Supplemental zinc and vitamin A can alleviate negative effects of heat stress in broiler chickens. Biol Trace Elem Res 94: 225-235.
Lambert, G. P. 2004. Role of gastrointestinal permeability in exertional heatstroke. Exerc Sport Sci Rev 32: 185-190.
Lambert, G. P. 2009. Stress-induced gastrointestinal barrier dysfunction and its inflammatory effects. J Anim Sci 87: E101-108.
Lambert, G. P., Gisolfi, C. V., Berg, D. J., Moseley, P. L., Oberley, L. W. & Kregel, K. C. 2002. Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress. J Appl Physiol 92: 1750-1761; discussion 1749.

LeBlanc, S. J., K. E. Leslie, and T. F. Duffield. 2005. Metabolic predictors of displaced abomasum in dairy cattle. J Dairy Sci 88: 159-170.
Leon, L.R. 2007. Heat stroke and cytokines. Prog Brain Res 162, 481-524.
Lim, C. L., G. Wilson, L. Brown, J. S. Coombes, and L. T. Mackinnon. 2007. Pre-existing inflammatory state compromises heat tolerance in rats exposed to heat stress. Am J Physiol Regul Integr Comp Physiol 292: R186-194.
Lima, A. A., Brito, L. F., Ribeiro, H. B., Martins, M. C., Lustosa, A. P., Rocha, E. M., Lima, N. L., Monte, C. M. & Guerrant, R. L. 2005. Intestinal barrier function and weight gain in malnourished children taking glutamine supplemented enteral formula. J Pediatr Gastroenterol Nutr 40: 28-35.
Loeb, G. A., D. C. Skelton, T. D. Coates, and H. J. Forman. 1988. Role of selenium-dependent glutathione peroxidase in antioxidant defenses in rat alveolar macrophages. Exp Lung Res 14 Suppl: 921-936.
Luber, G., and M. McGeehin. 2008. Climate change and extreme heat events. American Journal of Preventive Medicine 35: 459-467.
Ludvigsson, J. F., P. Elfström, U. Broomé, A. Ekbom, and S. M. Montgomery. 2007. Celiac disease and risk of liver disease: a general population-based study. Clin Gastroenterol Hepatol 5: 63-69.e61.
Mallonée, P. G., D. K. Beede, R. J. Collier, and C. J. Wilcox. 1985. Production and physiological responses of dairy cows to varying dietary potassium during heat stress. J Dairy Sci 68: 1479-1487.
Mao, X., S. Qi, B. Yu, J. He, J. Yu, and D. Chen. 2013. Zn(2+) and L-isoleucine induce the expressions of porcine beta-defensins in IPEC-J2 cells. Mol Biol Rep 40,1547-1552.
Marchbank, T., G. Davison, J.R. Oakes, M.A. Ghatei, M. Patterson, M.P Moyer, and R.J. Playford. 2011. The nutriceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes. Am J Physiol Gastrointest Liver Physiol 300, G477-484.
McArt, J. A., D. V. Nydam, P. A. Ospina, and G. R. Oetzel. 2011. A field trial on the effect of propylene glycol on milk yield and resolution of ketosis in fresh cows diagnosed with subclinical ketosis. J Dairy Sci 94: 6011-6020.
Metcalf, J. A., Crompton, L. A., Wray-Cahen, D., Lomax, M. A., Sutton, J. D., Beever, D. E., MacRae, J. C., Bequette, B. J., Backwell, F. R. & Lobley, G. E. 1996. Responses in milk constituents to intravascular administration of two mixtures of amino acids to dairy cows. J Dairy Sci 79: 1425-1429.
Miele, L., Valenza, V., La Torre, G., Montalto, M., Cammarota, G., Ricci, R., Mascianà, R., Forgione, A., Gabrieli, M. L., Perotti, G., Vecchio, F. M., Rapaccini, G., Gasbarrini, G., Day, C. P. & Grieco, A. 2009. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 49: 1877-1887.
Mishra, M., F. A. Martz, R. W. Stanley, H. D. Johnson, J. R. Campbell, and E. Hilderbrand. 1970. Effect of diet and ambient tempeature-humidity on ruminal pH, oxidation reduction potential, ammonia and lactic acid in lactating cows. J Anim Sci 30:1023.

Moody, E. G., P. J. Van Soest, R. E. McDowell, and G. L. Ford. 1967. Effect of high temperature and dietary fat on performance of lactating cows. J Dairy Sci 50: 1909-1916.
Moore, C. E., J. K. Kay, R. J. Collier, M. J. Vanbaale, and L. H. Baumgard. 2005. Effect of supplemental conjugated linoleic acids on heat-stressed brown swiss and holstein cows. J Dairy Sci 88: 1732-1740.
Nayeri, A., N.C. Upah, M.V. Sanz-Fernandez, E. Sucu, A.L. Gabler, R.L. Boddicker, D.B. Snider, J.M. Defrain, L.H. Baumgard. 2012. Characterizing the temporal and seasonal pattern of plasma lipopolysaccharide binding protein during the transition period. J Anim Sci 90 E-Suppl. 3: 666
Nilipoul, A. 1998. Betafin improves performance of broilers exposed to high ambient temperature and fed diets reduced in methionine and choline chloride. World Poultry 14: 26-27.
O'Brien, M. D., R. P. Rhoads, S. R. Sanders, G. C. Duff, and L. H. Baumgard. 2010. Metabolic adaptations to heat stress in growing cattle. Domest Anim Endocrinol 38: 86-94.
Ominski, K. H., A. D. Kennedy, K. M. Wittenberg, and S. A. Moshtaghi Nia. 2002. Physiological and production responses to feeding schedule in lactating dairy cows exposed to short-term, moderate heat stress. J Dairy Sci 85: 730-737.
Ospina, P. A., D. V. Nydam, T. Stokol, and T. R. Overton. 2010. Association between the proportion of sampled transition cows with increased nonesterified fatty acids and beta-hydroxybutyrate and disease incidence, pregnancy rate, and milk production at the herd level. J Dairy Sci 93: 3595-3601.
Oztürk, C., Avlan, D., Cinel, I., Cinel, L., Unlü, A., Camdeviren, H., Atik, U. & Oral, U. 2002. Selenium pretreatment prevents bacterial translocation in rat intestinal ischemia/reperfusion model. Pharmacol Res 46: 171-175.
Packer, J., T. Slater, and R. Willson. 1979. Direct observation of a free radical interaction between vitamin E and vitamin C. Nature 278: 737-738.
Padilla, L., and T. Matsuia. 2006. Heat stress decreases plasma vitamin C concentration in lactating cows. Livestock Science 101: 300-304.
Parlesak, A., C. Schäfer, T. Schütz, J. C. Bode, and C. Bode. 2000. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. J Hepatol 32: 742-747.
Pearce, S.C., N.K. Gabler, J.W. Ross, J. Escobar, J.F. Patience, R.P. Rhoadsm, and L.H. Baumgard. 2013a. The effects of heat stress and plane of nutrition on metabolism in growing pigs. J Anim Sci 91:2108-18.
Pearce, S.C., V. Mani, R.L. Boddicker, R.P. Rhoads, T.E. Weber, J.W. Ross, L.H. Baumgard and N.K. Gabler. 2013. Heat stress reduces intestinal barrier integrity and favors intestinal glucose transport in growing pigs. PLOS-ONE.: 1;8(8):e70215.
Peterson, S. E., S. E., Rezamand, P., Williams, J. E., Price, W., Chahine, M. & McGuire, M. A. 2012. Effects of dietary betaine on milk yield and milk composition of mid-lactation Holstein dairy cows. J Dairy Sci 95: 6557-6562.

Playford, R.J., D.N. Floyd, C.E. Macdonald, D.P. Calnan, R.O. Adenekan, W. Johnson, R.A. Goodlad, and T. Marchbank. 1999. Bovine colostrum is a health food supplement which prevents NSAID induced gut damage. Gut 44, 653-658.

Playford, R.J., C.E. MacDonald, D.P. Calnan, D.N. Floyd, T. Podas, W. Johnson, A.C. Wicks, O. Bashir, and T. Marchbank. 2001. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. Clin Sci (Lond)100, 627-633.

Pollman, D. 2010. Seasonal effects on sow herds: Industry experience and management strategies. (abstract). 88. p 9, Journal of Animal Science.

Prosser, C., K. Stelwagen, R. Cummins, P. Guerin, N. Gill, and C. Milne. 2004. Reduction in heat-induced gastrointestinal hyperpermeability in rats by bovine colostrum and goat milk powders. J Appl Physiol 96, 650-654.

Rao, L., B. Puschner, and T. A. Prolla. 2001. Gene expression profiling of low selenium status in the mouse intestine: transcriptional activation of genes linked to DNA damage, cell cycle control and oxidative stress. J Nutr 131: 3175-3181.

Rhoads, R.P., L.H. Baumgard, J.K. Saugee and S.R. Sanders. 2013. Nutritional interventions to alleviate the negative consequences of heat stress. Adv. Nutr. 4:267-276.

Rhoads, M. L., Rhoads, R. P., VanBaale, M. J., Collier, R. J., Sanders, S. R., Weber, W. J., Crooker, B. A. & Baumgard, L. H. 2009a. Effects of heat stress and plane of nutrition on lactating Holstein cows: I. Production, metabolism, and aspects of circulating somatotropin. J Dairy Sci 92: 1986-1997.

Rhoads RP, Sanders SR, Cole L, Skrzypek MV, Elsasser TH, Duff GC, Collier RJ, Baumgard LH. 2009b. Effects of heat stress on glucose homeostasis and metabolic response to an endotoxin challenge in Holstein steers. J Anim Sci 87 E-Suppl. 2:78.

Rollwagen, F.M., S. Madhavan, A.Singh, Y.Y. Li, K. Wolcott, and R. Maheshwari. 2006. IL-6 protects enterocytes from hypoxia-induced apoptosis by induction of bcl-2 mRNA and reduction of fas mRNA. Biochem Biophys Res Commun 347, 1094-1098.

Sahin, K., O. Kucuk, N. Sahin, and M. Sari. 2002a. Effects of vitamin C and vitamin E on lipid peroxidation status, serum hormone, metabolite, and mineral concentrations of Japanese quails reared under heat stress (34 degrees C). Int J Vitam Nutr Res 72: 91-100.

Sahin, K., N. Sahin, S. Yaralioglu, and M. Onderci. 2002b. Protective role of supplemental vitamin E and selenium on lipid peroxidation, vitamin E, vitamin A, and some mineral concentrations of Japanese quails reared under heat stress. Biol Trace Elem Res 85: 59-70.

Sanz-Fernandez, M.V., S.C. Pearce, N.K. Gabler, J.F. Patience, M.E. Wilson, M.T. Socha, J.L. Torrison, R.P. Rhoads and L.H. Baumgard. 2014. Effects of supplemental zinc amino acid complex on gut integrity in heat-stressed growing pigs. Animal. 8:43-50.

Shwartz, G., M. Rhoads, M. VanBaale, R. Rhoads, and L. Baumgard. 2009. Effects of a supplemental yeast culture on heat-stressed lactating Holstein cows. Journal of Dairy Science 92: 935-942.

Silanikove, N., F. Shapiro, and D. Shinder. 2009. Acute heat stress brings down milk secretion in dairy cows by up-regulating the activity of the milk-borne negative feedback regulatory system. BMC Physiol 9: 13.
Singh, P. K. Wise, S. Y., Ducey, E. J., Fatanmi, O. O., Elliott, T. B. & Singh, V. K. 2012. α-Tocopherol succinate protects mice against radiation-induced gastrointestinal injury. Radiat Res 177: 133-145.
Singleton, K. D., and P. E. Wischmeyer. 2006. Oral glutamine enhances heat shock protein expression and improves survival following hyperthermia. Shock 25: 295-299.
Solga, S. F., and A. M. Diehl. 2003. Non-alcoholic fatty liver disease: lumen-liver interactions and possible role for probiotics. J Hepatol 38: 681-687.
Sprong, R.C., A.J. Schonewille, and R. van der Meer. 2010. Dietary cheese whey protein protects rats against mild dextran sulfate sodium-induced colitis: role of mucin and microbiota. J Dairy Sci 93, 1364-1371.
St. Pierre, N., B. Cobanov, and G. Schnitkey. 2003. Economic losses from heat stress by US livestock industries. Journal of Dairy Science 86: E52-E77.
Stazi, A. V., and B. Trinti. 2008. Selenium deficiency in celiac disease: risk of autoimmune thyroid diseases. Minerva Med 99: 643-653.
Sturniolo, G.C., V. Di Leo, A. Ferronato, A. D'Odorico, and R. D'Incà. 2001. Zinc supplementation tightens "leaky gut" in Crohn's disease. Inflamm Bowel Dis 7, 94-98.
Thurnham, D. I., C. A. Northrop-Clewes, F. S. McCullough, B. S. Das, and P. G. Lunn. 2000. Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants. J Infect Dis 182 Suppl 1: S23-28.
VanBaale, M., J. Smith, M. Brouk, and L. Baumgard. 2005. Evaluate the efficacy of your cooling system through core body temperature Hoards Dairyman. p 147-148.
Varga, G., and M. Pickett. 2002. Strategies for feeding the transition cow. In: Southwest Dairy Nutrition Conference, Houston, TX
Waldron MR, Kulick AE, Bell AW, Overton TR. 2006. Acute experimental mastitis is not causal toward the development of energy-related metabolic disorders in early postpartum dairy cows. J Dairy Sci 89:596-610.
Wang, X., M.C. Valenzano, J.M. Mercado, E.P. Zurbach, and J.M. Mullin. 2013. Zinc Supplementation Modifies Tight Junctions and Alters Barrier Function of CACO-2 Human Intestinal Epithelial Layers. Dig Dis Sci 58, 77-87.
West, J. 2002. Physiological effects of heat stress on production and reproduction. In: Tri-State Dairy Nutrition Conference. p 1-9.
West, J. W. 2003. Effects of heat-stress on production in dairy cattle. J Dairy Sci 86: 2131-2144.
Wheelock, J. B., R. P. Rhoads, M. J. Vanbaale, S. R. Sanders, and L. H. Baumgard. 2010. Effects of heat stress on energetic metabolism in lactating Holstein cows. J Dairy Sci 93: 644-655.
Yang, Y., Y. Yuan, Y. Tao, and W. Wang. 2011. Effects of vitamin A deficiency on mucosal immunity and response to intestinal infection in rats. Nutrition 27: 227-232.

Zhang, B., and Y. Guo. 2009. Supplemental zinc reduced intestinal permeability by enhancing occludin and zonula occludens protein-1 (ZO-1) expression in weaning piglets. Br J Nutr 102, 687-693.
Zimbelman, R. B., L. H. Baumgard, and R. J. Collier. 2010. Effects of encapsulated niacin on evaporative heat loss and body temperature in moderately heat-stressed lactating Holstein cows. J Dairy Sci 93: 2387-2394.