Impact of Chronic Inflammation on the Health of Dairy Cattle, Swine, and Beef Cattle

E.J. Mayorga, E.H. Horst, S.K. Kvidera, M. Alqaisi, M.A. Abeyta, S. Rodriguez-Jimenez, B.M. Goetz, and L.H. Baumgard

Iowa State University, Department of Animal Science, Ames, IA 50011

Corresponding author: Lance H. Baumgard

313 Kildee Hall, Ames, IA

baumgard@iastate.edu

2019 Pacific Northwest Animal Nutrition Conference Proceedings

Introduction

There are a variety of situations in an animal's life where nutrient utilization is reprioritized from productive towards agriculturally unproductive purposes. Heat stress represents one of these annual situations where productivity is markedly reduced in all animal agriculture. Decreased feed intake experienced during heat stress is unable to fully explain decreases in productivity. Additionally, animals exposed to a thermal load exhibit altered post-absorptive metabolism, characterized by increased basal and stimulated circulating insulin. While the metabolism of heat stress has been thoroughly studied for the last 40 years, the initial insult in the cascade of events ultimately reducing productivity in heat-stressed animals has not been identified. Although certainly multifactorial, many of the negative consequences of heat stress on animal health and productivity may be mediated by reduced intestinal integrity. To that end, we have generated preliminary data strongly implicating a metabolic disruptor, endotoxin, as the etiological culprit of environmental hyperthermia. Endotoxin initiates an immune response characterized by inflammation, and both acute and chronic inflammation require a substantial amount of nutrients (amino acids and glucose).

Heat Stress

Many reports indicate the global surface temperature is expected to increase (IPCC, 2007). High ambient temperature, especially when coupled with elevated humidity, imposes severe thermal stress and reduces performance in all agriculturally important species (Baumgard et al., 2011, Baumgard and Rhoads, 2013; Belhadj Slimen et al., 2015). Heat stress interferes with animal comfort and suppresses production efficiency (Fuquay, 1981; Strong et al., 2015). Furthermore, it is well-known that genetically selecting animals based on productivity increases their metabolic heat production which makes them less heat resistant. In other words, increased production decreases heat tolerance (Brown-Brandl et al., 2004; Spiers et al., 2004). Despite advances in management practices and nutritional mitigation strategies, heat stress continues to be a financial burden. In the U.S. livestock industry, annual losses associated with environmental

hyperthermia are estimated to be nearly $900 million for dairy, $369 million for beef, and $1 billion for swine (St. Pierre, 2003; Pollmann, 2010). These economic constraints are mainly explained by the negative consequences of heat stress on productive parameters including milk yield and composition, growth, reproduction, and carcass traits (Baumgard and Rhoads, 2013).

During periods of heat stress, animals initiate major thermo-regulatory adaptations in order to maintain euthermia. It has traditionally been assumed that inadequate feed intake caused by the thermal load was responsible for decreased milk production (Fuquay, 1981; West, 2003; Strong et al., 2015). Presumably, reduced feed intake is a survival strategy as digesting and processing nutrients generates heat, especially in ruminants (i.e., thermic effect of feed; Collin et al., 2001; West, 2003). However, reduced feed intake only explains approximately 35-50% of the decreased milk yield during environmental-induced hyperthermia (Rhoads et al., 2009; Wheelock et al., 2010; Baumgard et al., 2011). Therefore, heat stress affects many production parameters either indirectly (i.e., via decreased feed intake; Collier et al., 2006; Adin et al., 2009; Hansen 2009; Baumgard et al., 2011, Baumgard and Rhoads, 2013; Mahjoubi et al., 2014) or directly (i.e., decreased milk yield, increased mortality). Direct mechanisms contributing to heat stress milk yield losses involve an altered endocrine profile, including reciprocal changes in circulating anabolic and catabolic hormones (Bernabucci et al., 2010; Baumgard and Rhoads, 2012). Such changes are characterized by increased circulating insulin, lack of adipose tissue lipid mobilization, and reduced adipocyte responsiveness to lipolytic stimuli. Cellular bioenergetics in the liver and skeletal muscle also exhibit clear differences in carbohydrate production and use due to heat stress. Thus, the heat stress response markedly alters post-absorptive carbohydrate, lipid, and protein metabolism through coordinated changes in fuel supply and utilization across tissues in a manner distinct from commonly recognizable changes that occur in animals on a reduced plane of nutrition (Baumgard and Rhoads, 2013). Altogether, the result of heat stress is underachievement of an animal's full genetic potential.

Heat stress and leaky gut

Mechanisms responsible for altered nutrient partitioning during heat stress are not clear; however, they might be mediated by the effects of heat stress on gastrointestinal health and function as we and others have demonstrated heat stress compromised intestinal barrier function (Lambert et al., 2002; Dokladny et al., 2006; Pearce et al., 2013; Sanz Fernandez et al., 2014). During heat stress, blood flow is diverted from the viscera to the periphery in an attempt to dissipate heat, 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., 2013). As a result, heat stress increases the passage of luminal content into portal and systemic blood (Hall et al., 2001; Pearce et al., 2013). Endotoxin, otherwise referred to as lipopolysaccharide (LPS), is a glycolipid embedded in the outer membrane of Gram-negative bacteria, which are abundant and prolific in luminal content, and is a well-characterized potent immune stimulator in multiple species (Berczi et al., 1966; Giri et al., 1990; Tough et al., 1997). Activation of the immune system occurs when LPS binding protein (LBP) initially binds LPS and together with CD14 and

TLR4 delivers LPS for removal and detoxification, thus LBP is frequently used as a biomarker for LPS infiltration (Ceciliani et al., 2012). For a detailed description of how livestock and other species detoxify LPS see our recent review (Mani et al., 2012). Endotoxin infiltration into the bloodstream during heats tress is a common observation among heat stroke patients (Leon, 2007) and is thought to play a central role in heat stroke pathophysiology as survival increases when intestinal bacterial load is reduced or when plasma LPS is neutralized (Bynum et al., 1979; Gathiram et al., 1987). It is remarkable how animals suffering from heat stroke or severe endotoxemia share many physiological and metabolic similarities to heats tress, such as increase 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 steers and pigs and demonstrated > 10-fold increase in circulating insulin (Kvidera et al., 2016, 2017b,c). Interestingly, increased insulin occurs prior to increased inflammation and the temporal pattern agrees with our previous in vivo data and a recent in vitro report (Bhat et al., 2014) suggesting LPS stimulates insulin secretion, either directly or via GLP-1 (Kahles et al., 2014). The possibility that LPS increases insulin secretion likely explains the hyperinsulinemia we have repeatedly reported in a variety of heat-stressed agriculture models (Baumgard and Rhoads, 2013). Again, the increase in insulin in both models is energetically difficult to explain as feed intake was severely depressed in both experiments (Figure 1).

Leaky gut's contribution to decreased animal productivity

Distinguishing between the direct and indirect effects of leaky gut on metabolism and productivity is difficult as situations responsible for decreased intestinal integrity are highly variable in nature (i.e., heat stress, transition period). Therefore, to isolate leaky gut and evaluate its effects on metabolism, production, and inflammation, we intentionally induced intestinal permeability in otherwise healthy mid-lactation dairy cows using a gamma secretase inhibitor (GSI), a compound that specifically inhibits crypt stem cell differentiation into enterocytes via disrupting Notch signaling (van Es et al., 2005). We anticipated feed intake of GSI-administered cows would decrease, so we pair-fed controls in order to eliminate the confounding effect of dissimilar feed intake. Treatment with GSI decreased feed intake and altered jejunum morphology consistent with characteristics of leaky gut (shortened crypt depth, decreased villus height, decreased villus height to crypt depth ratio). Circulating insulin and LBP were increased in GSI cows relative to controls. Interestingly in our GSI model, acute phase proteins serum amyloid A and haptoglobin increased for both GSI and pair-fed treatments over time, indicating inflammation was occurring in pair-fed controls as well (Kvidera et al., 2017a). This is not surprising, as pair-fed controls were receiving ~20% of their ad libitum intake and decreased feed intake has been shown to increase intestinal permeability in feed restricted rodents and humans (Rodriguez et al., 1996; Welsh et al., 1998).

This is of particular relevance as suboptimal feed intake, either voluntarily (i.e., weaning, heat stress, transition period, phycological stress) or involuntarily (i.e., off-feed events, drought, shipping, overcrowding) is a common observation in animal production settings. In fact, we've repeatedly reported reduced intestinal barrier integrity in thermal neutral pigs that were pair-fed to their heat-stressed counterparts (Pearce et al., 2013; Sanz Fernandez et al., 2014). Therefore, to further elucidate the effects

of feed restriction alone, we subjected mid-lactation cows to different levels of feed restriction. Results from this study confirmed the detrimental effects of feed restriction by demonstrating a linear increase in circulating acute phase proteins and endotoxin with increasing severity of feed restriction. Furthermore, cows fed 40% of ad libitum intake had shortened ileum villous height and crypt depth, indicating reduced intestinal health (Kvidera et al., 2017d).

Ketosis and its association with leaky gut

The periparturient period is associated with substantial metabolic changes involving normal homeorhetic adaptations to support milk production (Baumgard et al., 2006; Baumgard et al., 2017). Unfortunately, a disproportionate amount of herd culling occurs before cows reach 60 days in milk (Godden, 2003). Ketosis is defined as an excess of circulating ketone bodies and is characterized by decreases in feed intake, milk production, and increased risk of developing other transition period diseases (Chapinal et al., 2012). Epidemiological data indicate about 20% of transitioning dairy cows clinically experience ketosis (BHBA > 3.0 mM; Gillund et al., 2001) while the incidence of subclinical ketosis (>1.2 mM BHBA) is thought to be much higher (> 40%; McArt et al., 2012). Ketosis is a costly disorder (estimated at ~$300 per case; McArt et al., 2015) and thus it represents a major hurdle to farm profitability. Traditionally, ketosis is thought to result from excessive adipose tissue mobilization (Baird, 1982; Grummer, 1993; Drackley, 1999) which in turn contributes to fatty liver (hepatic steatosis) and excessive ketone body synthesis (Grummer, 1993). However, our recent study demonstrated increased inflammatory markers in cows diagnosed with ketosis only and no other health disorders. When compared with healthy controls, ketotic cows had increased circulating LPS prior to calving and post-partum acute phase proteins such as LPS-binding protein, serum amyloid A, and haptoglobin were also increased (Figure 2; Abuajamieh et al., 2016). Although endotoxin can originate from a variety of locations and obvious sources in transitioning dairy cows include the uterus (metritis), and mammary gland (mastitis) (Mani et al., 2012), we believe intestinal permeability may also be responsible for inflammation observed in the transition dairy cow.

Metabolism of inflammation

LPS-induced inflammation has an energetic cost which redirects nutrients away from anabolic process that support milk and muscle synthesis (see review by Johnson, 1997, 1998) and thus compromises productivity and efficiency. Interestingly, immune cells become more insulin sensitive and consume copious amounts of glucose upon activation in order to support rapid proliferation and biosynthetic processes (Calder et al., 2007; Palsson-McDermott and O'Neill, 2013). In contrast, inflammation induces an insulin resistant state in skeletal muscle and adipose tissue (Liang et al., 2013; Poggi et al., 2007). Recent data has also demonstrated a decrease in ketone oxidation during LPS infiltration (Suagee et al., 2011; Frisard et al., 2015) which we believe may partly explain increased ketone body concentrations during the transition period.

Endotoxin has previously been recognized to be involved with metabolic dysfunction. In humans, both obesity and high fat diets are linked to endotoxemia (Cani et al., 2007, Gregor and Hotamisligil, 2011). Furthermore, LPS is involved with the development of fatty liver (Ilan, 2012), and cytokines are linked to lipid accumulation and cholesterol retention (Ma et al., 2008; Clément et al., 2008). Experimentally-induced endotoxemia in dairy cattle has been linked to several metabolic and endocrine disturbances including decreased circulating glucose, termination of pregnancy, leukopenia, disruption of ruminal metabolism, and altered calcium homeostasis (Griel et al., 1975; Giri et al., 1990; Waldron et al., 2003; Jing et al., 2014). The aforementioned pathological conditions are likely mediated by LPS-induced inflammation and the subsequent changes in nutrient partitioning caused by immune system activation.

What are the energetic costs of immune activation?

The energetic costs of immunoactivation are substantial. Upon activation, immune cells become obligate glucose utilizers and switch their metabolism from oxidative phosphorylation to aerobic glycolysis in a phenomenon known as the Warburg Effect (Vander Hiden et al., 2009). Although quantifying the energetic demand of the immune system is difficult due to its ubiquitous nature, we have recently employed a series of LPS-euglycemic clamps to calculate the energetic cost of an activated immune system. Using this model, we estimated glucose consumption by an activated immune system in lactating Holstein cows, growing steers, and growing pigs. Interestingly, on a metabolic body weight basis the amount of glucose utilized by LPS-activated immune system in lactating cows, growing steers, and growing pigs was 0.64, 1.0, and 1.1 g glucose/kg $BW^{0.75}$/h, respectively (Kvidera et al., 2016, 2017b,c). Additional data generated in two separated studies in lactating cows revealed a similar number (1.0 and 0.93 g/kg BW^{075}; Horst et al., 2018a,b), suggesting the response is conserved across species and life stages. A limitation to our model is the inability to account for liver's contribution to the circulating glucose pool (i.e., glycogenolysis and gluconeogenesis). However, both glycogenolytic and gluconeogenic rates have been shown to be increased during infection (Spitzer et al., 1985; Waldron et al., 2003). Furthermore, we have observed both increased circulating glucagon and cortisol (indirect markers of hepatic glucose output) following LPS administration (Horst et al., 2018c,d) suggesting we are underestimating the energetic cost of immunoactivation.

Conclusion

Increased immune system glucose utilization occurs simultaneously with infection-induced decreased feed intake: this coupling of enhanced nutrient requirements with hypophagia obviously decrease the amount of nutrients available for the synthesis of valuable products (milk, meat, fetus). We and others have now demonstrated that both heat-stressed and ketotic animals have increased circulating endotoxin and markers of inflammation. We believe that circulating LPS in both maladies originates from the intestine and thus both likely have an activated immune system. This inflammation can redirect resources normally used for growth, milk production, muscle synthesis, and reproduction toward agriculturally unproductive purposes. More research is still needed to understand the mechanisms and consequences

of intestinal permeability and associated inflammation in order to provide foundational information for developing strategies aimed at maintaining productivity under these circumstances.

*Parts of this manuscript were first published in the proceedings of the 2016, 2017 and 2018 Southwest Nutrition Conference in Tempe AZ.

References

Abuajamieh, M., S.K. Kvidera, M.V. Fernandez, A. Nayeri, N.C. Upah, E.A. Nolan, S.M. Lei, J.M. DeFrain, H.B. Green, K.M. Schoenberg, E.B. Trout, and L.H. Baumgard. 2016. Inflammatory biomarkers are associated with ketosis in periparturient Holstein cows. Res. Vet. Sci. 109:81-85.

Adin, G., A. Gelman, R. Solomon, I. Flamenbaum, M. Nikbachat, E. Yosef, A. Zenou, A. Shamay, Y. Feuermann, S. J. Mabjeesh, and J. Miron. 2009. Effects of cooling dry cows under heat load conditions on mammary gland enzymatic activity, intake of food water, and performance during the dry period and after parturition. Livest. Sci. 124:189–195.

Baird, G.D. 1982. Primary ketosis in the high-producing dairy cow: clinical and subclinical disorders, treatments, prevention and outlook. J. Dairy Sci. 65:1-10.

Baumgard, L.H., R.J. Collier and D.E. Bauman. 2017. Invited Review: Regulation of nutrient partitioning to support lactation. J. Dairy Sci. 100:10353-10366.

Baumgard, L.H., L.J. Odens, J.K. Kay, R.P. Rhoads, M.J. VanBaale and R.J Collier. 2006. Does negative energy balance (NEBAL) limit milk synthesis in early lactation? Proc. Southwest Nutr. Conf. 181-187.

Baumgard, L.H. and R.P. Rhoads. 2013. Effects of heat stress on postabsorptive metabolism and energetics. Annu. Rev. Anim. Biosci. 1:311–337.

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

Belhadj Slimen, I., T. Najar, A. Ghram, and M. Abdrrabba. 2015. Heat stress effects on livestock: molecular, cellular and metabolic aspects, a review. J Anim. Physiol. Anim. Nutr.

Berczi, I., L. Bertok, and T. Bereznai. 1966. Comparative studies on the toxicity of Escherichia coli lipopolysaccharide endotoxin in various animal species. Can. J. of Microbiol. 12:1070-1071.

Bernabucci U., N. Lacetera, L.H. Baumgard, R.P. Rhoads, B. Ronchi, and A. Nardone. 2010. Metabolic and hormonal acclimation to heat stress in domesticated ruminants. Animal. 4:1167-1183.

Bhat, U.G., V. Ilievski, T.G. Unterman, and K. Watanabe. 2014. Porphyromonas gingivalis lipopolysaccharide (LPS) upregulates insulin secretion from pancreatic beta cells line MIN6. J. Periodontol. 85:1629–1636.

Brown-Brandl, T. M., J. A. Nienaber, H. Zin, and S. Gates. 2004. A literature review of swine heat production. Trans. ASAE 47:259–270.

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.

Calder, P.C., G. Dimitriadis, and P. Newsholme. 2007. Glucose metabolism in lymphoid and inflammatory cells and tissues. Curr. Opin. Clin. Nutr. Metab. Care. 10:531-540.

Cani, P.D., J. Amar, M.A. Iglesias, M. Poggi, C. Knauf, D. Bastelica, A.M. Neyrinck, F. Fava, K.M. Tuohy, C. Chabo, A. Waget, E. Delmée, B. Cousin, T. Sulpice, B. Chamontin, J. Ferrières, J.F. Tanti, G.R. Gibson, L. Casteilla, N.M. Delzenne, M.C. Alessi, and R. Burcelin. 2007. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 56:1761-1772.

Ceciliani, F., J.J. Ceron, P.D. Eckersall, and H. Sauerwein. 2012. Acute phase proteins in ruminants. J. Proteomics 75:4207-4231.

Chapinal, N., S.J. Leblanc, M.E. Carson, K.E. Leslie, S. Godden, M. Capel, J.E. Santos, M.W. Overton, and T.F. Duffield. 2012. Herd-level association of serum metabolites in the transition period with disease, milk production, and early lactation reproductive performance. J. Dairy Sci. 95:5676-5682.

Clément, S., C. Juge-Aubry, A. Sgroi, S. Conzelmann, V. Pazienza, B. Pittet-Cuenod, C.A. Meier, and F. Negro. 2008. Monocyte chemoattractant protein-1 secreted by adipose tissue induces direct lipid accumulation in hepatocytes. Hepatology. 48:799-807.

Collier, R. J., G. E. Dahl, and M. J. VanBaale. 2006. Major advances associated with environmental effects on dairy cattle. J. Dairy Sci. 89:1244–1253.

Collin, A., J. van Milgen, S. Dubois, and J. Noblet. 2001. Effect of high temperature on feeding behaviour and heat production in group-housed young pigs. Br. J. Nutr. 86:63–70.

Dokladny, K., P.L. Moseley, and T.Y. Ma. 2006. Physiologically relevant increase in temperature causes an increase in intestinal epithelial tight junction permeability. Am. J. Physiol. Gastrointest. Liver Physiol. 290: G204-G212.

Drackley, J.K. 1999. Biology of dairy cows during the transition period: the final frontier? J. Dairy Sci. 82: 2259–2273.

Frisard, M.I., Y. Wu, R.P. McMillan, K.A. Voelker, K.A. Wahlberg, A.S. Anderson, N. Boutagy, K. Resendes, E. Ravussin, and M.W. Hulver. 2015. Low levels of lipopolysaccharide modulate mitochondrial oxygen consumption in skeletal muscle. Metabolism 64:416-427.

Fuquay, J. W. 1981. Heat stress as it affects animal production. J. Anim. Sci. 52:164–174.

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.

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.

Giri, S.N., P. Emau, J.S. Cullor, G.H. Stabenfeldt, M.L. Bruss, R.H. Bondurant, and B.I. Osburn. 1990. Effects of endotoxin infusion on circulating levels of eicosanoids, progesterone, cortisol, glucose and lactic acid, and abortion in pregnant cows. Vet. Microbiol. 21:211-231.

Godden, S.M., S.C. Stewart, J.F. Fetrow, P. Rapnicki, R. Cady, W. Weiland, H. Spencer, and S.W. Eicker. 2003. The relationship between herd rbST supplementation and other factors and risk for removal

for cows in Minnesota Holstein dairy herds. Pp. 55-64 in Proc. Four-State Nutrition Conference. MidWest Plan. Service, LaCrosse, WI.

Gregor, M.F. and G.S. Hotamisligil. 2011. Inflammatory mechanisms in obesity. Annu. Rev. Immunol. 29:415–445.

Griel, L.C., A. Zarkower, and R.J. Eberhart. 1975. Clinical and clinico-pathological effects of Escherichia coli endotoxin in mature cattle. Can. J. Comp. Med. 39:1-6.

Grummer, R.R. 1993. Etiology of lipid-related metabolic disorders in periparturient dairy cows. J. Dairy Sci. 76:3882–3896.

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– H521.

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-G1203.

Hansen, P. J. 2009. Effects of heat stress on mammalian reproduction Philos. Trans. R. Soc. Lond. B. Biol. Sci. 364:3341–3350.

Horst, E.A., S. K. Kvidera, E.J. Mayorga, C.S. Shouse, M. Al-Qaisi, M.J. Dickson, J. Ydstie, H.A. Ramirez Ramirez, A.F. Keating, D.J. Dickson, K.E. Griswold, and L.H. Baumgard. 2018aEffect of chromium on bioenergetics and leukocyte dynamics following immunoactivation in lactating Holstein cows. J. Dairy. Sci. 101:5515-5530.

Horst, E.A., E. J. Mayorga, S. L. Portner, M. Al-Qaisi, C. S. McCarthy, M. A. Abeyta, B. M. Goetz, H. A. Ramirez-Ramirez, D. H. Kleinschmit, and L. H. Baumgard. 2018b. Effects of dietary zinc on energetic requirements of an activated immune system following lipopolysaccharide challenge in lactating cows. J. Dairy Sci. J. Dairy Sci. 101 (Suppl. 2): 271.

Horst, E. A., E. J. Mayorga, S. L. Portner, M. Al-Qaisi, C. S. McCarthy, M. A. Abeyta, B. M. Goetz, H. A. Ramirez-Ramirez, D. H. Kleinschmit, and L. H. Baumgard. 2018c. Effects of dietary zinc source on inflammatory biomarkers and PMN function following lipopolysaccharide challenge in lactating cows. J. Dairy Sci. (Suppl. 2): 383

Horst, E. A., E. J. Mayorga, M. Al-Qaisi, M. A. Abeyta, S. L. Portner, C. S. McCarthy, B. M. Goetz, H. A. Ramirez-Ramirez, and L. H. Baumgard. 2018d. Effects of maintaining eucalcemia following immunoactivation in lactating cows. J. Dairy Sci. (Suppl. 2):383

Ilan, Y. 2012. Leaky gut and the liver: a role for bacterial translocation in nonalcoholic steatohepatitis. World J. Gastroenterol. 18:2609-2618.

Intergovernmental Panel on Climate Change (IPCC). 2007. The Intergovernmental Panel on Climate Change 4th assessment report. www.ipcc.ch/. Accessed May 12, 2015.

Jing, L., R. Zhang, Y. Liu, W. Zhu, and S. Mao. 2014. Intravenous lipopolysaccharide challenge alters ruminal bacterial microbiota and disrupts ruminal metabolism in dairy cattle. Br. J. Nutr. 112:170-182.

Johnson, R.W. 1998. Immune and endocrine regulation of food intake in sick animals. Dome. Animal Endo. 15: 309-319.

Johnson, R.W. 1997. Inhibition of growth by pro-inflammatory cytokines: an integrated view. J Anim. Sci. 75: 1244-1255.

Kahles, F., C. Meyer, J. Möllmann, S. Diebold, H.M. Findeisen, C. Lebherz, C. Trautwein, A. Koch, F. Tacke, N. Marx, and M. Lehrke. 2014. GLP-1 Secretion Is Increased by Inflammatory Stimuli in an IL-6–Dependent Manner, Leading to Hyperinsulinemia and Blood Glucose Lowering. Diabetes. 63:3221-3229.

Kvidera, S.K., M.J. Dickson, M. Abuajamieh, D.B. Snider, M.V. Sanz-Fernandez, J.S. Johnson, A.F. Keating, P.J. Gorden, H.B. Green, K.M. Schoenberg, and L.H. Baumgard. 2017a. Intentionally induced intestinal barrier dysfunction causes inflammation, affects metabolism, and reduces productivity in lactating Holstein cows. J. Dairy Sci. 100:4113-4127.

Kvidera, S.K., E.A. Horst, M. Abuajamieh, E.J. Mayorga, M.V. Sanz-Fernandez, and L.H. Baumgard. 2017b. Glucose requirements of an activated immune system in lactating Holstein cows. J. Dairy Sci. 100:2360-2374.

Kvidera, S.K., E.A. Horst, E.J. Mayorga, M.V. Sanz-Fernandez, M. Abuajamieh, and L.H. Baumgard. 2017c. Estimating glucose requirements of an activated immune system in growing pigs. J. Anim. Sci. 95:5020-5029.

Kvidera, S.K., E.A. Horst, M.V. Sanz-Fernandez, M. Abuajamieh, S. Ganesan, P.J. Gorden, H.B. Green, K.M. Schoenberg, W.E. Trout, A.F. Keating, and L.H. Baumgard. 2017d. Characterizing effects of feed restriction and glucagon-like peptide 2 administration on biomarkers of inflammation and intestinal morphology. J. Dairy Sci. 100:9402-9417.

Kvidera, S.K., E.A. Horst, M. Abuajamieh, E.J. Mayorga, M.V. Sanz-Fernandez, and L.H. Baumgard. 2016. Technical note: A procedure to estimate glucose requirements of an activated immune system in steers. J. Anim. Sci. 94:4591-4599.

Lambert, G.P., C.V. Gisolfi, D.J. Berg, P.L. Moseley, L.W. Oberley, and K.C. Kregel. 2002. Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress. J. Appl. Physiol. 92:1750-1761.

Leon, L.R. 2007. Heat stroke and cytokines. Prog. Brain Res. 162:481-524.

Liang, H., S.E. Hussey, A. Sanchez-Avila, P. Tantiwong, and N. Musi. 2013. Effect of lipopolysaccharide on inflammation and insulin action in human muscle. PLoS One 8:e63983.

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.

Ma, K.L., X.Z. Ruan, S.H. Powis, Y. Chen, J.F. Moor- head, and Z. Varghese. 2008. Inflammatory stress exacerbates lipid accumulation in hepatic cells and fatty livers of apolipoprotein E knockout mice. Hepatology. 48:770-781.

Mahjoubi, E., H. Amanlou, H. R. Mirzaei-Alamouti, N. Aghaziarati, M. Hossein Yazdi, G. R. Noori, K. Yuan and L. H. Baumgard. 2014. The effect of cyclical and mild heat stress on productivity and metabolism in Afshari lambs. J. Anim. Sci. 92:1007-1014

Mani, V., T.E. Weber, L.H. Baumgard and N.K. Gabler. 2012. Growth and development symposium: endotoxin, inflammation, and intestinal function in livestock. J. Anim. Sci. 90:1452-1465.

McArt, J.A., D.V. Nydam, and M.W. Overton. 2015. Hyperketonemia in early lactation dairy cattle: A deterministic estimate of component and total cost per case. J. Dairy Sci. 98:2043-2054.

McArt, J.A., D.V. Nydam, and G.R. Oetzel. 2012. Epidemiology of subclinical ketosis in early lactation dairy cattle. J. Dairy Sci. 95:5056-5066.

Palsson-McDermott, E.M. and L.A. O'Neill. 2013. The Warburg effect then and now: from cancer to inflammatory diseases. Bioessays 35:965-973.

Pearce, S.C., V. Mani, T.E. Weber, R.P. Rhoads, J.F. Patience, L.H. Baumgard, and N.K. Gabler. 2013. Heat stress and reduced plane of nutrition decreases intestinal integrity and function in pigs. J. Anim. Sci. 91:5183-5193.

Poggi, M., D. Bastelica, P. Gual, M.A. Iglesias, T. Gremeaux, C. Knauf, F. Peiretti, M. Verdier, I. Juhan-Vague, J.F. Tanti, R. Burcelin, and M.C. Alessi. 2007. C3H/HeJ mice carrying a toll-like receptor 4 mutation are protected against the development of insulin resistance in white adipose tissue in response to a high-fat diet. Diabetologia 50:1267-1276.

Pollmann, D. S. Seasonal effects on sow herds: industry experience and management strategies. 2010. J. Anim. Sci. 88 (Suppl. 3) (Abstr.)

Rhoads, M. L., R. P. Rhoads, M. J. VanBaale, R. J. Collier, S. R. Sanders, W. J. Weber, B. A. Crooker, and L. H. Baumgard. 2009. 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.

Rodriguez, P., N. Darmon, P. Chappuis, C. Candalh, M. A. Blaton, C. Bouchaud and M. Heyman. 1996. Intestinal paracellular permeability during malnutrition in guinea pigs: effect of high dietary zinc. Gut 39:416–422.

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.

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.

Spiers, D. E., J. N. Spain, J. D. Sampson, and R. P. Rhoads. 2004. Use of physiological parameters to predict milk yield and feed intake in heat-stressed dairy cows. J. Therm. Biol. 29:759–764.

St. Pierre, N. R., B. Cobanov, and G. Schnitkey. 2003. Economic losses from heat stress by US livestock industries. J. Dairy Sci. 86:E52–E77.

Strong, R. A., E. B. Silva, H. W. Cheng, and S. D. Eicher. 2015. Acute brief heat stress in late gestation alters neonatal calf innate immune functions. J. Dairy Sci. 98:1–13.

Suagee, J.K., B.A. Corl, J.G. Wearn, M.V. Crisman, M.W. Hulver, R.J. Geor, and L.J. McCutcheon. 2011. Effects of the insulin-sensitizing drug pioglitazone and lipopolysaccharide administration on insulin sensitivity in horses. J. Vet. Intern. Med. 25:356-364.

Tough, D.F., S. Sun, and J. Sprent. 1997. T cell stimulation in vivo by lipopolysaccharide (LPS). J. Exp. Med. 185:2089-2094.

van Es, J.H., M.E. van Gijn, O. Riccio, M. van den Born, M. Vooijs, H. Begthel, M. Cozijnsen, S. Robine, D.J. Winton, F. Radtke, and H. Clevers. 2005. Notch/gamma-secretase inhibition turns proliferative cells in intestinal crypts and adenomas into goblet cells. Nature. 435:959–963.

Vander Heiden, M.G., L.C. Cantley, and C.B. Thompson. 2009. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 324:1029-1033.

Waldron, M.R., A.E. Kulick, A.W. Bell, and T.R. Overton. 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.

Waldron, M.R., B.J. Nonnecke, T. Nishida, R.L. Horst, and T.R. Overton. 2003. Effect of lipopolysaccharide infusion on serum macromineral and vitamin D concentrations in dairy cows. J. Dairy Sci. 86:3440-3446.

Welsh, F.K., S.M. Farmery, K. MacLennan, M.B. Sheridan, G.R. Barclay, P.J. Guillou, J.V. Reynolds. 1998. Gut barrier function in malnourished patients. Gut. 42:396-401.

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.

Figures

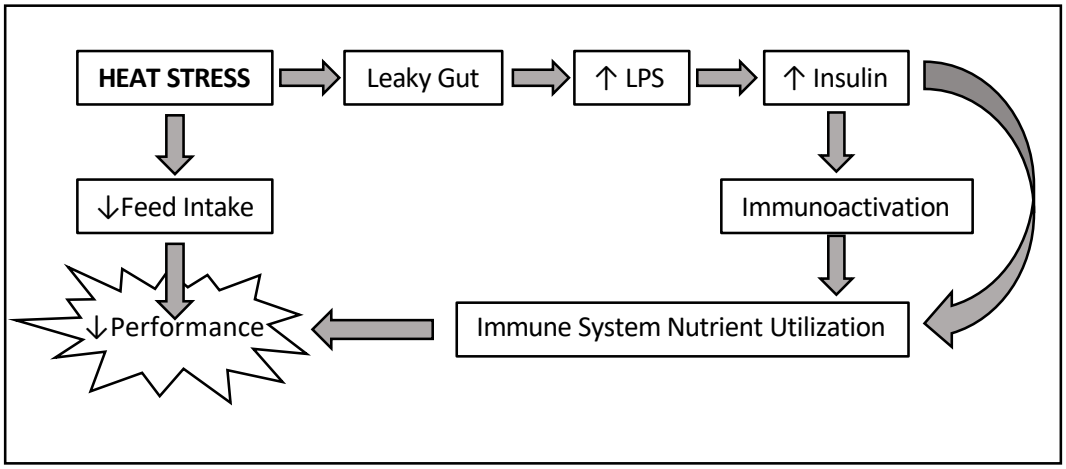

Figure 1. Consequences of leaky gut on metabolism and inflammation during heat stress.

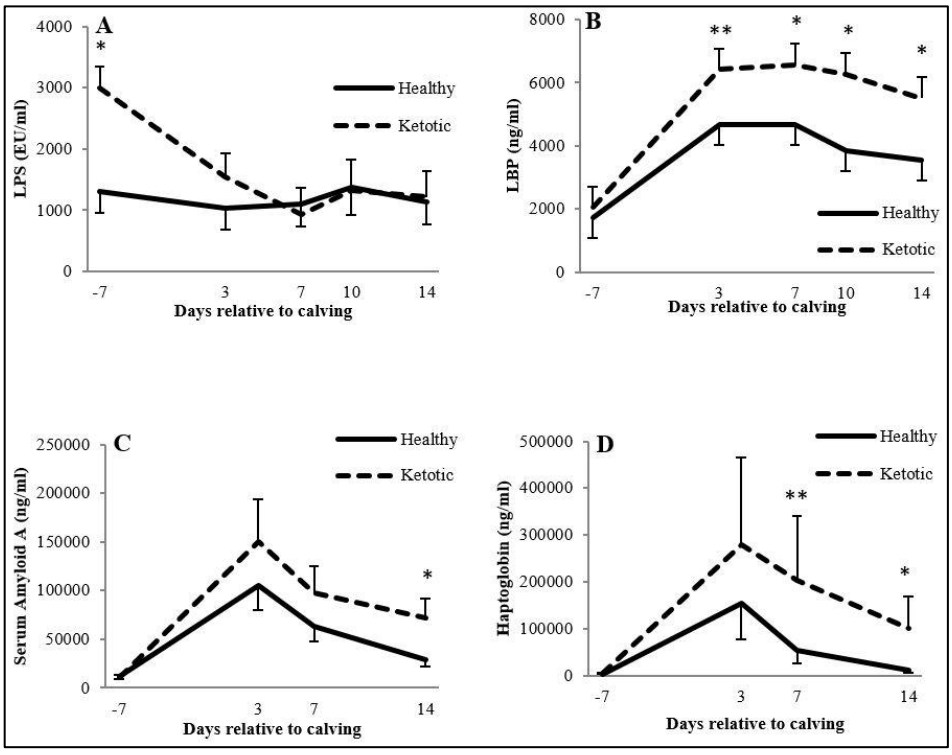

Figure 2. Markers of inflammation in healthy (solid line) and ketotic (dashed line) transition cows.

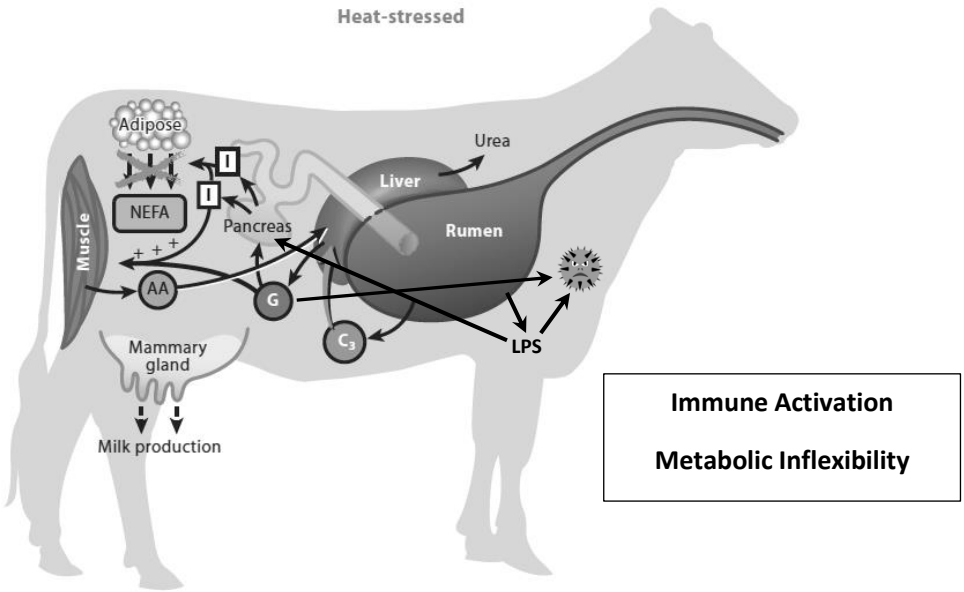

Figure 3. Nutrient partitioning in a heat-stressed lactating cow. Intestinal dysfunction resulting from heat stress results in lipopolysaccharide (LPS) translocation into portal and systemic circulation. Immunoactivation and the subsequent inflammatory increase glucose uptake by immune cells. The pancreas secretes more insulin preventing the cow from sparing glucose for milk synthesis. The heat-stressed cow enters a metabolically inflexible state characterized by minimal use of body fat reserves. Abbreviations: AA, amino acids; C_3, propionate; E, energy, G. glucose; I, insulin, LPS; lipopolysaccharide; NEFA, nonesterified fatty acid. (Adapted from Baumgard and Rhoads, 2013).