# Re-evaluating dogmas of metabolic health in transition cows

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**Introduction:** There are a variety of situations in a farm animal's life when nutrient utilization is prioritized towards agriculturally unproductive purposes. Two well-known examples that markedly reduce production efficiency are heat stress and ketosis. Decreased feed intake, experienced during both situations, is unable to fully explain the decreased productivity. Additionally, both ketosis and heat stress are characterized by negative energy balance, body weight loss, inflammation, and hepatic steatosis. While the metabolism of ketosis and heat stress have been thoroughly studied for the last 40 years, the initial insult in the cascade of events ultimately reducing productivity in both heat-stressed and ketotic cows has not been identified. To that end, our data strongly implicates intestinally derived endotoxin as the etiological culprit in each case.

**Ketosis:** The periparturient period is associated with substantial metabolic changes involving normal homeorhetic adaptations to support milk production. Unfortunately, a disproportionate amount of herd culling occurs before cows reach 60 days in milk (NAHMS, 2008). Ketosis is arbitrarily 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).

**Heat Stress:** Heat stress negatively impacts a variety of production parameters and is a significant financial burden to animal agriculture. Heat-stress affects productivity indirectly by reducing feed intake; however, direct mechanisms also contribute as we have shown reduced feed intake only explains approximately 35-50% of the decreased milk yield during heat stress (Rhoads et al., 2009; Wheelock et al., 2010; Baumgard et al., 2011). Direct mechanisms contributing to heat stress milk yield losses involve an altered endocrine profile, including reciprocal changes in circulating anabolic and catabolic hormones (Collier et al., 2006; Bernabucci et al., 2010; Baumgard and Rhoads, 2012). Such changes are characterized by increased circulating insulin concentration, lack of adipose tissue lipid mobilization, and reduced adipocyte responsiveness to lipolytic stimuli. Hepatic and skeletal muscle cellular bioenergetics also exhibit clear differences in carbohydrate production and use, respectively, 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).

**Endotoxin: The Common Denominator?:** Endotoxin, otherwise referred to as lipopolysaccharide (LPS) is a glycolipid embedded in the outer membrane of Gram-negative bacteria and is a well-characterized potent immune stimulator in multiple species (Berczi et al., 1966; Giri et al., 1990; Tough et al., 2007). LPS-induced inflammation redirects nutrients away from anabolic processes that support milk and muscle synthesis (see review by Johnson, 1997, 1998) and thus compromises productivity and efficiency. Initial mechanisms responsible for altered nutrient partitioning during heat stress may be mediated by inflammation resulting from effects of heat stress on gastrointestinal health and function (Baumgard and Rhoads, 2013). As a result, heat stress increases the infiltration of luminal LPS into the portal and systemic blood (Hall et al., 2001; Pearce et al., 2013b). Furthermore, 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). Likewise, increased inflammatory markers following parturition have been reported in cows (Ametaj et al., 2005; Bertoni et al., 2008; Humblet et al., 2006; Mullins et al., 2012). We have demonstrated increased inflammation prior to ketosis diagnosis and in cows with no overt infection in the uterus or mammary gland (Abuajamieh et al., 2015). Endotoxin can originate from a variety of locations, and obvious sources in transitioning dairy cows include the uterus, mammary gland, and the gastrointestinal tract (Mani et al., 2012). We have demonstrated decreased milk synthesis during a pharmaceutical-induced model of leaky gut (Stoakes et al., 2014) and have also shown a simple 60% feed restriction alters gut morphology and increases circulating LPS (Stoakes et al., 2015a). Furthermore, experimentally-induced endotoxemia in dairy cattle has been linked to several metabolic and endocrine disturbances including decreased circulating glucose, abortion, 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). Our data and the literature suggest the aforementioned pathological conditions in both heat stress and ketosis are likely mediated by LPS-induced inflammation and the subsequent changes in nutrient partitioning caused by immune system activation.

**Energetic Cost of Immune System Activation:** Upon immune system activation, immune cells switch their metabolism from oxidative phosphorylation to aerobic glycolysis, causing them to become obligate glucose utilizers in a phenomenon known as the Warburg Effect (Vander Hiden et al., 2009). Our group recently employed a series of LPS-euglycemic clamps to quantify the energetic cost of an activated immune system. Using this model, we estimated approximately 1 kg of glucose is used by the immune system during a 12 hour period in lactating dairy cows. 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 is 0.64, 1.0, and 1.1 g glucose/kg $BW^{0.75}$/h, respectively; Stoakes et al., 2015b,c,d). 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, wool, etc.).

**Conclusion:** Ketosis and heat stress are two of the most economically important pathologies which severely jeopardize the competitiveness of animal agriculture. Heat stress and ketosis affect herds of all sizes and almost every dairy region of the globe. We suggest, based upon the literature and on our supporting evidence, that LPS is the common etiological origin of both metabolic disorders. Collectively, we hypothesize that leaky gut and the resulting LPS markedly alters nutrient partitioning and is a causative agent in metabolic disruption during heat stress and ketosis. Identifying dietary approaches that can ameliorate gut barrier dysfunction is paramount in developing seasonal mitigating strategies.

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