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Effects of Heat Stress on Postabsorptive Metabolism and Energetics

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Abstract

Environmental-induced hyperthermia compromises efficient animal production and jeopardizes animal welfare. Reduced productive output during heat stress was traditionally thought to result from decreased nutrient intake. Our observations challenge this dogma and indicate that heat-stressed animals employ novel homeorhetic strategies to direct metabolic and fuel selection priorities independent of nutrient intake or energy balance. Alterations in systemic physiology support a shift in carbohydrate metabolism, evident through changes such as basal and stimulated circulating insulin levels. Hepatocyte and myocyte metabolism also show clear differences in glucose production and use during heat stress. Perhaps most intriguing, given the energetic shortfall of the heat-stressed animal, is the apparent lack of fat mobilization from adipose tissue coupled with a reduced responsiveness to lipolytic stimuli. Thus, the heat stress response markedly alters postabsorptive carbohydrate, lipid, and protein metabolism independently of reduced feed intake through coordinated changes in fuel supply and utilization by multiple tissues.

INTRODUCTION

Suboptimal livestock productivity limits animal agriculture's competitiveness and marginalizes efforts to reduce inputs into food production. The US meat and dairy industries have made efficient production a high priority and, as a result, have realized rapid improvements in milk yield and lean growth of market animals. Unfortunately, heat stress (HS) undermines genetic, nutritional, pharmaceutical, and management advances made by the animal agriculture industries. 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 (for, e.g., milk or meat) is deemphasized.

Heat stress negatively impacts a variety of productive parameters including milk yield and composition, growth, reproduction, and carcass traits. In addition, a heat load increases health care costs, and animals can even succumb to severe thermal stress (especially lactating cows and animals without shade). A 2006 California heat wave purportedly resulted in the deaths of more than 30,000 dairy cows (1), and a recent heat wave in Iowa killed at least 4,000 head of beef cattle (2). Furthermore, almost 50% of Canadian summer days are environmentally stressful to dairy cows (3). This illustrates that most geographical locales, including temperate and northern climates, are susceptible to extreme and lethal heat. Therefore, environmental HS is a significant financial burden (~$900 m/year for dairy and > $300 m/year for beef and swine in the United States alone) (4, 5). Advances in management (e.g., cooling systems, barn construction) have alleviated some negative impacts that thermal stress inflicts on animal agriculture, but production still decreases during the summer (6, 7). Consequently, HS is one of the costliest issues facing progressive animal producers and certainly one of the primary hurdles to efficient animal agriculture in developing countries.

The detrimental effects of HS on animal welfare and production will likely become more of an issue if earth's climate continues to warm as predicted (8), and some models forecast extreme summer conditions in most animal-producing areas in the United States (9). Apart from its direct effects on animal metabolism and physiology (described below), much of the detrimental effects of climate change on global animal productivity will be mediated indirectly by reduced feed availability and quality, increased disease occurrence, and increased susceptibility to parasites and vector-borne disease. For example, climate changes will likely limit livestock's access to pasture and forage availability owing to heat-induced decreased yield, drought, extreme temperature changes, and elevated CO_2 (10). In addition, global warming is expected to adversely impact the biodiversity and distribution of microflora, which will likely increase the emergence of zoonotic agents and infectious disease outbreaks (11).

Changing human demographics and locations of economic growth and affluence will likely also dictate where livestock production will need further developing. The human population continues to increase, especially in the tropical and subtropical areas of the planet (12). As a result, animal agriculture in these warm areas will need to expand (13) to keep pace with the global appetite for high-quality protein. However, many countries in these geographical areas are still developing and may lack facilities and resources required for effective heat-abatement strategies. At the very least, HS will continue to regionalize animal agriculture to more moderate environmental conditions within a specific country, and these areas frequently are far from the population base (i.e., Southeast Asia). Therefore, HS is likely one of the primary (if not the principal) factor(s) limiting efficient animal protein production and will continue to compromise food security in developing countries.

Owing to the physics of animal heat dissipation, genetic selection based on traditional production traits also may contribute to a decreased tolerance to HS (14). Basal/metabolic heat production increases with enhanced production [i.e., enhanced milk yield (15) and lean tissue accretion (16)]. Consequently, an animal or a breed's annual productivity must be considered before introducing novel genetics into a particular geography (17).

Thus, for a variety of aforementioned reasons, there is an urgent need to better understand how HS alters nutrient utilization and ultimately reduces animal productivity. Defining the biology and mechanisms of how HS jeopardizes animal performance is critical in developing approaches to ameliorate current production issues. And it is a prerequisite for generating future mitigating strategies (genetic, managerial, nutritional, and pharmaceutical) to improve animal well-being and performance, to ensure a constant supply of animal products for human consumption, and to secure and enhance the global agriculture economy.

PRODUCTION RESPONSES

Lactation

Milk synthesis is incredibly sensitive to thermal stress; for example, decreased yields of 35–40% are not unusual in dairy cows (18). This is not unique to dairy cattle, as lactation performance in sows is reduced markedly during HS (19). (For a detailed description of how cows accumulate and dissipate heat and the etiology of HS development, see review articles 20 and 21.) It was traditionally thought lactating cows become heat stressed when conditions exceed a temperature humidity index (THI) of 72 (6). However, recent climate-controlled experiments indicate that milk yield starts to decrease at a THI of 68 (22). This is supported by field observations evaluating the THI when cow standing time (a ruminant response to a thermal load) increases (23). The lower THI at which cows are thought to become heat stressed is consistent with the hypothesis that higher-producing cows are more susceptible to a thermal load (24).

The mechanistic basis for environmental-induced hyperthermia milk-yield losses likely involves multiple systems. First, an altered endocrine profile, including reciprocal changes in circulating anabolic and catabolic hormones (discussed below), certainly contributes (10, 24, 25). Second, HS impacts numerous intracellular signaling pathways responsible for maintenance, productivity, and survival (26). Further, mammary epithelial cells likely are directly affected by hyperthermia, which has been shown clearly in vitro using extreme temperatures (42°C) (26). Finally, recent evidence indicates that a derivative of β-casein acts like a ligand and binds a receptor on the apical side of the mammary epithelial cell, which disrupts potassium channels and ultimately reduces milk synthesis (27). This is akin to the "feedback inhibition of lactation" concept (28) and implies that mammary epithelial cells are unable to utilize blood-derived milk-building blocks. If this system were a large contributor to HS-induced decreased milk yield, one would expect blood content of milk precursors (e.g., glucose) to increase. However, during HS, blood concentrations of key precursors of milk components are reduced, which is particularly evident for glucose (29, 30). Presumably, a direct effect on the mammary gland would result in parallel changes in the content of milk components, but this is not the case, because milk fat, protein, and lactose content change discordantly during acute HS (27, 31). Although HS likely negatively affects the mammary gland, we believe this direct action contributes little to the overall decrease in milk yield. Regardless, the net result of the aforementioned changes, coupled with marked decreases in nutrient intake, is an event highly coordinated to prioritize acclimation and survival. The exact contribution of each altered system to overall reduced milk yield is currently unknown.

Heat-stressed animals reduce feed intake, ostensibly as a survival strategy, because digesting and processing nutrients generates heat (i.e., thermic effect of feed), especially in ruminants (18). It has traditionally been assumed that inadequate feed intake caused by the thermal load is responsible for decreased milk production (18, 32–35). However, our recent results, in which we demonstrate disparate slopes in feed intake and milk-yield responses to a cyclical heat-load pattern, challenge this dogma (36). This led us to hypothesize that HS reduces milk synthesis by both direct and indirect (via reduced feed intake) mechanisms. To examine this hypothesis, we designed a series of pair-feeding experiments that enabled us to evaluate thermal stress while eliminating the confounding effects of dissimilar nutrient intake. This type of approach is required to differentiate between direct and indirect effects (e.g., reduced intake) of environmental-induced hyperthermia, because both heat-stressed and malnourished animals share common responses (e.g., reduced milk yield, growth, etc.). Our experiments demonstrate that reduced feed intake explains only approximately 35–50% of the decreased milk yield during environmental-induced hyperthermia (**Figure 1*a,b***) (29–31). Our results agree with previous data (37) and indicate that when overall HS (extent and duration) exceeds a given threshold (as-of-yet unidentified), the cumulative thermal load disrupts the nutrient intake–milk production relationship, and milk yield declines beyond expected levels.

Growth

Heat stress can also markedly reduce nutrient intake in growing animals. However, identifying how much of the decreased productivity is caused by the indirect compared with the direct effects of HS on growth is more difficult than in lactation models. This is primarily because the composition of tissue accretion is not considered when measuring gross changes in body weight gain. Therefore, reduced feed intake may appear to explain a majority of the performance decreases in growing animals, but the direct effects of heat may markedly alter the hierarchy of tissue synthesis.

Beef. In general, HS-induced production losses for beef cattle are not as severe as those experienced by the dairy industry. It is not entirely clear why growing cattle tolerate higher THI conditions and exhibit a greater heat-strain threshold than lactating dairy cows, but likely possibilities may include: (*a*) increased surface area–to-mass ratio, (*b*) reduced rumen heat production (because of the mostly grain diet), and (*c*) reduced overall metabolic heat production (on a body weight basis). In addition, beef cattle will often experience compensatory gain after mild or short periods of HS (38, 39). The combination of these factors translates into heat-related reduced gain that is typically less than 10 kg, which amounts to approximately seven extra days on feed (4). Furthermore, the impact of HS on reproductive indices is typically not as severe in beef cattle owing to the seasonal nature of breeding programs (which often occur during the spring in the United States).

Swine. The economic losses in the pig industry caused by a sustained thermal load include reduced growth and efficiency, increased health care costs, decreased carcass value (increased lipid and decreased protein), and increased mortality (especially in sows and market hogs). In addition, lactating sows and nursing piglets have drastically different thermal-neutral zones, which makes management difficult for this stage of production. Interestingly, the fact that pigs reared in HS conditions have reduced muscle mass and increased adipose tissue has been documented frequently over the past 40 years (40–46). This phenomenon is not unique to pigs; HS also alters carcass composition similarly in rodents (47, 48) and growing poultry (49–52).

A dramatic reduction in feed intake (up to 50%) is an obvious sign of HS and is thought to be primarily responsible for the negative effects HS has on pig performance (46). It is counterintuitive that HS causes a decrease in nutrient intake and depresses growth, yet increases carcass lipid

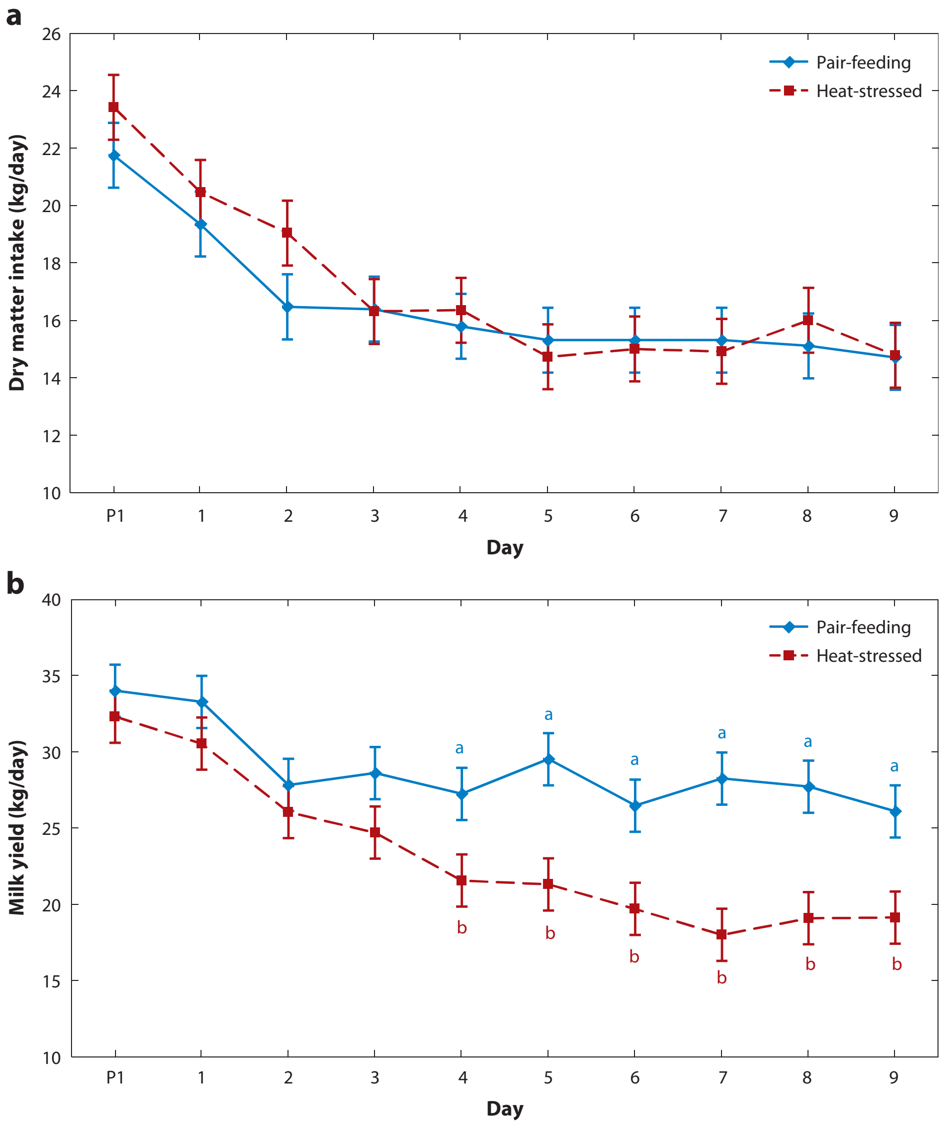

Figure 1

Effects of heat stress or pair-feeding on (*a*) dry matter intake and (*b*) milk yield in lactating Holstein cows. The mean value from days 1 to 9 of the thermal neutral ad libitum period (P1) was used as a covariate and is represented by P1 on the x axis. The results from days 1 to 9 are from period 2, when cows were exposed to heat stress or exposed to thermal-neutral conditions and pair-fed with the heat-stressed cows. Small a's and b's indicate that there are statistically significant differences between the data at $P < 0.01$. Adapted from Rhoads et al. (31).

accretion and decreases carcass nitrogen content. In thermal-neutral conditions, pigs consuming a restricted diet deposit protein at the expense of lipid accretion (i.e., the carcass lipid-to-protein ratio decreases, meaning the carcass becomes leaner), and the quantity of lipid deposited per unit of energy consumed decreases (53–55). Hence, the reduced feed intake–to–body composition relationship is exactly opposite in pigs reared in HS conditions and is independent of plane of nutrition. Despite its enormous economic impact, little is known about how HS directly and/or indirectly alters metabolism and nutrient partitioning in pigs.

Maintenance Costs

Heat stress is thought to increase maintenance requirements in rodents (56), poultry (57), sheep (58, 59), and cattle (33, 38, 60). The enhanced energy expenditure during HS is believed to originate from panting, sweating, and greater chemical reaction rates predicted by the van't Hoff–Arrhenius equation (32, 61). Furthermore, mounting a heat shock response comes at a substantial energetic cost, because producing heat shock proteins (HSPs) and maintaining their function as protein chaperones utilize a considerable amount of ATP (62). In addition, epinephrine is elevated during HS (especially during the early phase of hyperthermia) (33), and it markedly stimulates the Na^+/K^+ ATPase activity (63), which also requires a substantial quantity of ATP (64). The elevation in Na^+/K^+ ATPase activity was demonstrated recently in a variety of tissues from heat-stressed pigs (65). Although difficult to quantify, in lactating dairy cattle maintenance costs are estimated to be increased by as much as 25% during HS (66), and some suggest it may be greater than 30% (67). However, because heat-stressed animals typically have reduced circulating thyroid hormone concentrations (68–70), actual oxygen consumption (71) and energy expenditure/heat production may in fact decrease (16, 41, 72). Even textbooks often report that basal heat production is decreased whereas maintenance costs are increased during HS (61, 73). We find it difficult to envision how the two can occur simultaneously. Regardless, a quadratic relationship between environment and bioenergetics apparently exists in which maintenance costs and total body expenditure decline with mild HS but rapidly increase during severe HS, as suggested by others (51, 61). Adaptation also appears to influence energy expenditure during HS, as metabolic rates may increase during acute HS but decrease during chronic HS (37).

As stated earlier, the National Research Council arbitrarily suggests that mild to severe HS increases maintenance requirements by 7–25% but indicates that "insufficient data are currently available to quantify these effects accurately" (73a, p. 21). A typical lactating dairy cow has a maintenance requirement of 9.7 Mcal/day (or 0.08 Mcal/kg $BW^{0.75}$). In our pair-feeding experiments, ~8 kg of milk, which has an energetic value of approximately 6.1 Mcal/day, cannot be explained by the reduction in feed intake (**Figure 1**) (31). If all of the difference in milk synthesis (~8 kg/day) could be explained by the increase in maintenance requirements, then heat-stressed cows would have an increase in maintenance requirements of 63%. We are obviously unable to identify how much, if any, of the milk differential can be explained by enhanced maintenance costs, but if 25%, 50%, and 75% of the 6.1 Mcal/day was in fact utilized for increased maintenance, it would represent a 16%, 31%, and 47% increase in maintenance requirements, respectively. Quantifying the contribution of increased maintenance costs versus other altered biological systems (e.g., reduced nutrient absorption, altered endocrine status) toward the milk yield differential is of primary interest.

METABOLIC ADAPTATIONS TO REDUCED PLANE OF NUTRITION

A prerequisite for understanding metabolic adaptations that occur during HS is an appreciation for the physiological and metabolic adjustments that lactating and growing animals initiate during malnutrition. Collectively, changes in postabsorptive nutrient partitioning occur to support a dominant physiological state (i.e., milk and skeletal-muscle synthesis) (74), and one well-described homeorhetic strategy is the glucose-sparing effect that both lactating and growing animals utilize when on a lowered plane of nutrition or in negative energy balance (NEBAL).

Lactation

Early lactation dairy cattle enter a unique physiological state during which they cannot consume enough nutrients to meet maintenance and milk production costs, which causes the animals to enter into NEBAL (75). NEBAL is associated with a variety of metabolic changes that are implemented to support the dominant physiological condition of lactation (74). Marked alterations in both carbohydrate and lipid metabolism ensure partitioning of dietary- and tissue-derived nutrients toward the mammary gland (**Figure 2**). Not surprisingly, many of these changes are mediated by endogenous somatotropin, which naturally increases during periods of NEBAL (74). During NEBAL, somatotropin promotes nonesterified fatty acid (NEFA) export from adipose tissue by accentuating the lipolytic response to β-adrenergic signals and by inhibiting insulin-mediated lipogenesis and glucose utilization (76). The reduction in systemic insulin sensitivity is coupled with a decrease in circulating insulin levels, and this allows for adipose lipolysis and NEFA mobilization (74, 77). Increased circulating NEFA are typical in transitioning and malnourished cows, and they represent, along with NEFA-derived ketones, a significant source of energy (and precursors for milk-fat synthesis) for cows in NEBAL (**Figure 2**). Circulating NEFA have a very rapid turnover; thus, the severity of calculated NEBAL is positively associated with circulating NEFA levels (78, 79), and a linear relationship likely exists as a concentration-dependent process between NEFA delivery, tissue NEFA uptake, and NEFA oxidation (80). The magnitude of

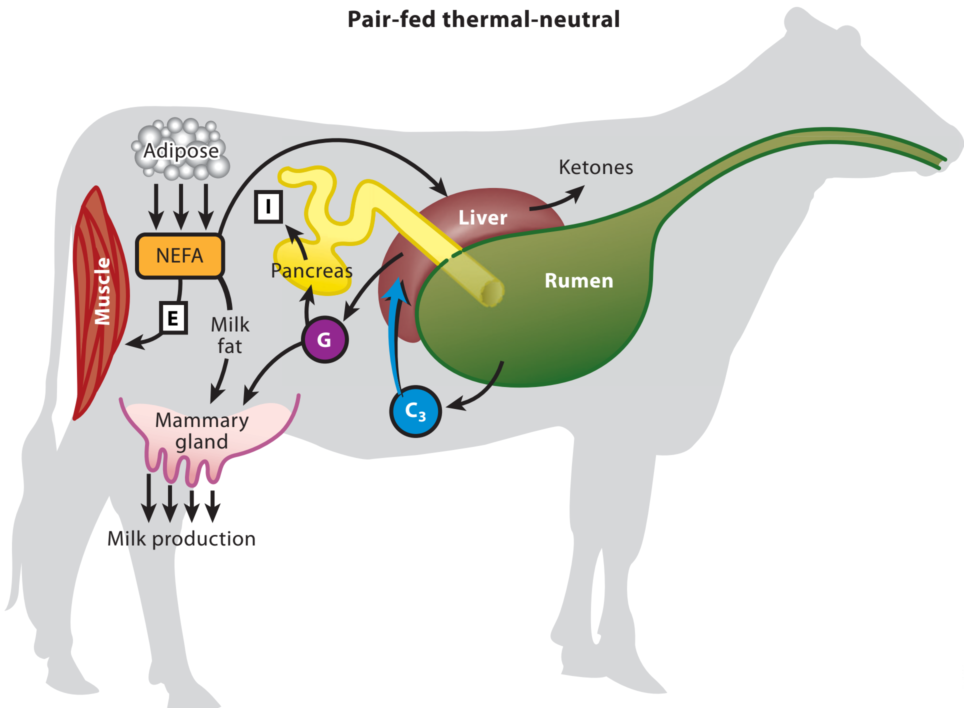

Figure 2

Nutrient partitioning in a thermal-neutral lactating cow on a restricted plane of nutrition. Reduced nutrient intake causes the pancreas to secrete less insulin and, coupled with reduced insulin sensitivity, creates a metabolically flexible state and allows the animal to spare glucose use for the synthesis of milk. Abbreviations: C_3, propionate; E, energy; G, glucose; I, insulin; NEFA, nonesterified fatty acid.

NEBAL, and thus lipid mobilization, in large part explains why cows lose considerable amounts (> 50 kg) of body weight during early lactation.

Postabsorptive carbohydrate metabolism is also markedly altered by NEBAL and is mediated mainly by reduced insulin action. During either early lactation or inadequate nutrient intake, glucose is partitioned toward the mammary gland, and glucose's contribution as a fuel source to extramammary tissues is decreased (81). The early lactation or NEBAL-induced hypoglycemia accentuates catecholamine's adipose lipolytic effectiveness (82). In this key glucose-sparing mechanism, referred to as the Randle Effect, elevated NEFA levels decrease skeletal muscle glucose uptake and oxidation (83). The fact that insulin simultaneously orchestrates both carbohydrate and lipid metabolism explains why there is a reciprocal relationship between glucose and NEFA oxidation. Ultimately, these are homeorhetic adaptations to maximize milk synthesis at the expense of tissue accretion (74). A thermal-neutral cow in NEBAL could be considered metabolically flexible, because it can depend upon alternative fuels (NEFA and ketones) to spare glucose, which can be utilized by the mammary gland for copious galactopoiesis.

Growth

Inadequate nutrient consumption during thermal-neutral conditions is associated with a variety of metabolic changes implemented to support the synthesis of high-priority tissues like skeletal muscle (54). Marked alterations in both carbohydrate and lipid metabolism ensure partitioning of dietary- and tissue-derived nutrients toward muscle, and altered concentrations of anabolic and catabolic signals mediate many of these changes. One characteristic response is a reduction in circulating insulin coupled with a decrease in adipose insulin sensitivity, which allows for adipose lipolysis and NEFA mobilization (84). Increased circulating NEFA are typical in restricted-fed animals and represent a significant source of energy. The enhanced fatty acid oxidation during nutrient restriction is a classic strategy to conserve glucose. Postabsorptive carbohydrate metabolism is also altered by reduced insulin action during feed restriction, resulting in reduced glucose uptake by adipose tissue. The reduced nutrient uptake coupled with the prolonged net release of NEFA by adipose tissue is a key homeorhetic mechanism implemented by malnourished pigs to prioritize protein synthesis (85).

POSTABSORPTIVE CHANGES DURING HEAT STRESS

Lipid Metabolism

Some production data suggest that HS alters metabolism differently than would be expected based upon calculated whole-body energy balance. For example, heat-stressed sows (69) and heifers (86) do not lose as much body weight and body condition, respectively, as their pair-fed, thermal-neutral counterparts do. In addition, carcass data indicate that rodents (47, 87), chickens (50), and pigs (41–44, 88) have increased lipid retention when reared in HS conditions. We and others have demonstrated that basal plasma NEFA levels are typically reduced in heat-stressed rodents (89), pigs (90), sheep (68), and cattle (36, 86) despite marked reductions in feed intake and especially when compared with pair-fed, thermal-neutral controls (**Figure 3*a***) (29, 31). Furthermore, we recently demonstrated that heat-stressed cows have a blunted NEFA response to an epinephrine challenge compared with pair-fed, thermal-neutral controls (**Figure 3*b***) (30). These observations agree with rodent data indicating that HS reduces in vivo lipolytic rates and in vitro lipolytic enzyme activity (91). The decreased NEFA levels during HS are unlikely to result from enhanced

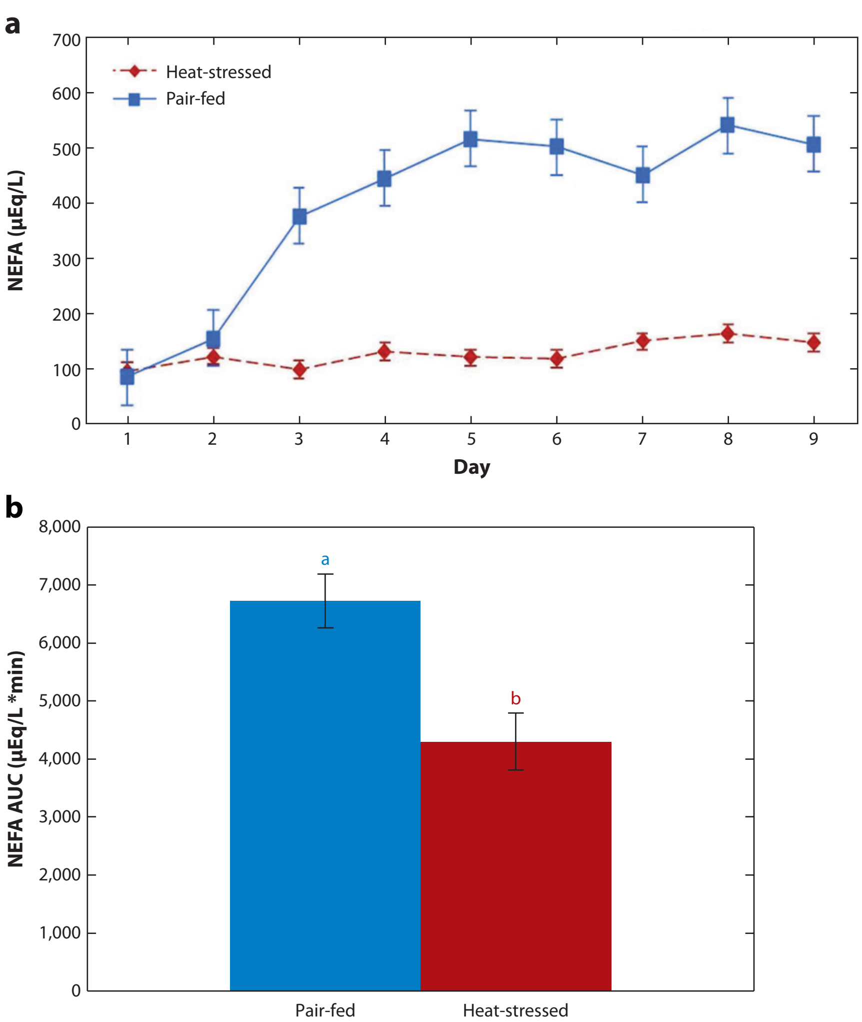

Figure 3

Effects of heat stress and pair-feeding (in thermal-neutral conditions) on (*a*) basal nonesterified fatty acid (NEFA) concentrations (31) and (*b*) NEFA response [calculated as area under the curve (AUC)] to an epinephrine challenge (30) in lactating Holstein cows. Small a's and b's indicate that there are statistically significant differences between the data at $P < 0.01$.

oxidation or an accelerated conversion of NEFA into ketones, because blood ketone concentration decreases and urine ketone content remains static with increasing ambient temperatures [Dale & Brody (1954); as reviewed in 20]. Moreover, HS increases adipose tissue lipoprotein lipase (89), which suggests that adipose tissue of hyperthermic animals has an increased capacity to uptake and store intestinal and hepatic-derived triglycerides. The changes in carcass composition, blood lipid profiles, and lipolytic capacity are surprising, because HS causes a well-described increase in stress and catabolic hormones [epinephrine, cortisol, glucagon; see reviews by Bianca (37) and Beede & Collier (33)]. The blunted lipolytic capacity of adipose tissue is especially unusual, because heat-stressed cows are severely nutrient restricted (30–40%), are in a calculated NEBAL (~5 Mcal; 29, 36, 92), and lose considerable amounts (>40 kg) of body weight (29, 31), all of which are parameters typically associated with elevated circulating NEFA levels (78, 79).

Carbohydrate Metabolism

Evidence from many species suggests that carbohydrate metabolism is altered during HS (93). For example, acute HS was first reported to cause hypoglycemia in cats. The condition was originally thought to underlie reduced worker/laborer productivity during warm summer months (94). In addition, human athletes exercising at high ambient temperatures consistently have increased hepatic glucose production and whole-body enhanced carbohydrate oxidation at the expense of lipids (95, 96). Furthermore, hepatic glucose production typically decreases after ingesting carbohydrates; however, exogenous sugars are unable to blunt HS-induced liver glucose output (97). The increased hepatic glucose output originates from increased glycogenolysis (96) and increased gluconeogenesis (56). Hepatic expression of the pyruvate carboxylase gene, a rate-limiting enzyme that controls lactate and alanine entry into the gluconeogenic pathway, is increased during HS in multiple animal models (98–101), and in hyperthermic rodents, lactate's contribution to gluconeogenesis increases (56, 102). Interestingly, plasma lactate concentrations rise during exercise in the heat (95, 97, 103), porcine malignant hyperthermia (102), heat-stressed growing steers (104), and heated melanoma cells (93). This presumably stems from skeletal-muscle efflux, but an increase in muscle lactate production and efflux is not the result of reduced muscle blood or oxygen flow (105). Collectively, these studies appear to indicate that peripheral tissues increase aerobic glycolysis, although the purpose of this altered metabolism and its contribution to cellular and system energetic homeostasis is unclear (see section on Glucose Sparing).

Our recent experiments in lactating dairy cows indicate that heat-stressed animals are secreting approximately 200–400 g less milk lactose per day compared with pair-fed, thermal-neutral controls (29, 31). The quantity of secreted lactose is generally equivalent to a similar amount (on a molar basis) of secreted glucose (even larger if the estimate of 72 g of glucose/kg of secreted milk is accurate) (106), but it is unclear whether the liver produces 200–400 g less glucose or if extramammary tissues utilize glucose at an increased rate. We have generated two lines of evidence indicating the latter. First, heat-stressed cows dispose of exogenous glucose quicker following a glucose tolerance test (29). Second, using stable isotopes, we have shown that whole-body glucose production (presumed to be primarily from hepatic tissue) and glucose response to an epinephrine challenge (used as a proxy for hepatic glycogenolytic sensitivity) do not differ between heat-stressed and pair-fed thermal-neutral controls (30), despite reports suggesting that the liver becomes partially dysfunctional during HS (87, 107, 108). As noted above, we recently reported that HS causes altered hepatic gluconeogenic gene expression, perhaps associated with a different precursor supply (101). As a consequence, it appears that the ruminant liver remains functional with regard to hepatic glucose output and that glucose is preferentially utilized for processes other than milk synthesis during HS.

Protein Metabolism

Heat stress also affects postabsorptive protein metabolism, as illustrated by changes in the quantity of carcass lean tissue in a variety of species (40, 47, 52). Muscle protein synthesizing machinery and RNA/DNA synthesis capacity are reduced by environmental hyperthermia (109), and similar effects apparently occur with regard to mammary α- and β-casein synthesis (110). Skeletal muscle catabolism is also clearly increased during HS, because numerous studies have reported increased plasma markers of muscle breakdown in a variety of species (29, 37, 51, 102, 111).

ENDOCRINE CHANGES

Somatotropin Axis

Somatotropin (growth hormone, GH) and insulin-like growth factor-I (IGF-I) are two of the most potent and well-characterized lactogenic hormones (77). Normally, somatotropin partitions nutrients toward the mammary gland by decreasing nutrient uptake by extramammary tissues and stimulating hepatic IGF-I synthesis and secretion. During NEBAL (e.g., early lactation), the somatotropic axis uncouples and hepatic IGF-I production decreases despite increased circulating somatotropin concentrations (112). We originally hypothesized that NEBAL caused by HS and early lactation differentially affects the somatotropic axis. For example, although acute HS increases somatotropin levels in birds (113) and steers (114), chronic heat-stressed cows (which are presumably in NEBAL) had or tended to have reduced somatotropin levels (115, 121). To evaluate this further, we analyzed basal somatotropin pulsatility characteristics and the pituitary's responsiveness to a somatotropin secretagogue and reported no differences in either parameter in HS versus pair-fed thermal-neutral controls (31). However, we did observe a modest reduction in circulating IGF-I, which may indicate that the metabolic milieu favors uncoupling of the somatotropic axis during HS (31). We investigated whether hepatic growth hormone (GH) responsiveness was altered during HS by measuring GH receptor abundance and signal transducer and activator of transcription 5 (STAT-5) phosphorylation (117). Heat stress, independent of reduced feed intake, decreased hepatic GH receptor abundance, although both HS and malnutrition were sufficient to decrease STAT-5 phosphorylation. Consistent with reduced GH signaling through STAT-5, hepatic IGF-I mRNA abundance was lower in heat-stressed animals. Thus, the reduced hepatic GH responsiveness observed during HS appears to involve mechanisms independent of reduced feed intake. The physiological significance of reduced hepatic GH receptor abundance during HS is unclear at this time but may serve to alter other GH-dependent hepatic processes, such as gluconeogenesis regulation. We hypothesize that reduced IGF-I may be one mechanism by which the liver and mammary tissues coordinate the reduction in milk synthesis so nutrients (e.g., glucose) can be utilized for other purposes, such as maintaining homeothermia.

Insulin

Despite hallmarks traditionally associated with hypoinsulinemia, such as (*a*) marked reductions in feed intake, (*b*) calculated NEBAL, and (*c*) rapid body weight loss (>40 kg), we have demonstrated that basal insulin concentrations gradually increase in lactating heat-stressed cows (29) and have confirmed this in growing heat-stressed calves (**Figure 4*a***) (118) and pigs (90). The increase in insulin, a potent anabolic hormone, during HS, an intensely catabolic condition, is seemingly a biological paradox. Increased plasma insulin concentrations in our experiments agree with data from another heat-stressed ruminant report (119), a malignant hyperthermic pig model (102), a heat-stressed rodent model (91), and other reports utilizing different insulin secretagogues (19, 119, 120). In addition, heat-stressed cows and calves have an increased insulin response to a glucose tolerance test (**Figure 4*b***) (29, 118). Reasons for hyperinsulinemia during HS are not clearly understood but likely include insulin's key role in activating and upregulating HSPs (121). Proper insulin signaling and action are strengthened by an effective heat-protective response (122). The lack of a NEFA response during HS may be a strategy to ensure the maintenance of elevated

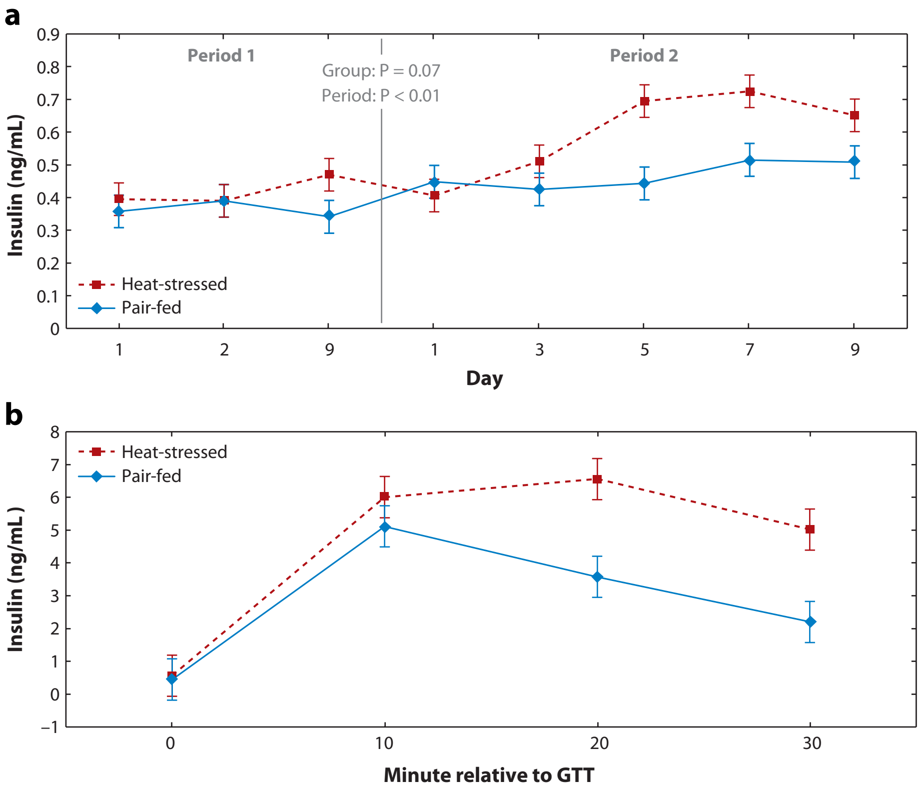

Figure 4

(*a*) Effects of heat stress and pair-feeding on basal insulin concentrations in growing Holstein bull calves. The vertical line separates period 1 (thermal-neutral conditions and ad libitum feed intake) from period 2 (either heat-stress conditions and ad libitum feed intake or thermal-neutral conditions and pair-feeding). (*b*) Effects of heat stress (ad libitum feed intake) and pair-feeding (thermal-neutral conditions) on the insulin response to a glucose tolerance test (GTT) in growing Holstein bull calves. Adapted from O'Brien et al. (118).

insulin parameters, because excessive NEFA causes pancreas β-cell apoptosis (123). Regardless of why, HS is one of the very few nondiabetic models we are aware of in which nutrient intake is markedly reduced but basal and stimulated insulin levels are increased.

The increased insulin may be an essential part of the HS-adaptation mechanism. For example, diabetic humans are more susceptible to heat-related illness and death (124, 125). Similarly, diabetic rats have an increased mortality rate when exposed to severe heat, and exogenous insulin increases their survival time (126). Furthermore, nonlethal HS ameliorates proxies of insulin insensitivity in diabetic rodents (127) or rodents fed high-fat diets (128). This is similar to reports indicating that thermal therapy (saunas and hot baths) improves insulin sensitivity in humans (129). One potential mechanism by which heat offers protection from insulin resistance is HSP72's ability to inhibit the activation of stress kinases c-Jun N-terminal kinase (JNK) and inhibitor of κB kinase β (IKKβ), which are enzymes involved in insulin resistance (130). Consequently, it appears that insulin and/or maintenance of insulin action plays a critical role in the ability to respond and ultimately survive a heat load.

The mechanisms signaling for enhanced insulin parameters during HS are not clear. One possibility is heat-induced hyperprolactinemia, which has been described in both genders and in multiple species (131) and was recently confirmed in pigs (132). In humans, severe HS increases prolactin more than threefold within 30 min (133). Although prolactin's role during established ruminant lactation is not clear (134), the increase in this lactogenic hormone during HS is paradoxical, given that milk yield is markedly reduced (18). The exact reason why HS increases prolactin is not known, but it may be involved with: the sweating response (135), HSP induction (136), altered water metabolism (20), and pelage molting (137). Prolactin may partially mediate HS-induced hyperinsulinemia as well. Prolactin was recently shown to increase in vitro pancreatic β cell proliferation (138) and in vivo glucose-stimulated insulin secretion (139), and consequently it is an active area of research in the diabetes field. The temporal pattern of heat-induced prolactin corresponds with the temporal pattern of increased circulating insulin (3–4 days), and it is tempting to speculate that prolactin is increasing pancreatic β cell proliferation and insulin secretion in agricultural species as well.

An additional signal for heat-induced increased circulating insulin may be endotoxin [i.e., lipopolysaccharide (LPS)]. Heat-stressed animals redistribute blood to the periphery in an attempt to maximize radiant heat dissipation. To maintain blood pressure during HS, the gastrointestinal tract vasculature vasoconstricts (140), and blood flow to the splanchnic tissues can decrease up to 50% (141, 142). Enterocytes are extremely sensitive to oxygen and nutrient restriction (143), and HS causes marked conformation changes and reduces intestinal barrier function (140, 142). We have demonstrated this in heat-stressed pigs (144), and it presumably occurs in heat-stressed ruminants as well. For a variety of reasons, HS causes rumen acidosis (145, 146), which, independent of HS, can compromise the integrity of the gastrointestinal tract barrier (147). Therefore, ruminants may actually be more prone than monogastrics to intestinal leakiness during HS. The increased paracellular transport of LPS from the lumen into circulation causes a local proinflammatory response and, if severe enough, can cause systemic endotoxemia (148, 149). Animals suffering from heat stroke or severe endotoxemia share many physiological and metabolic similarities (150). Infusing LPS into the mammary gland was first reported to increase (approximately twofold) circulating insulin in lactating cows (151). In addition, we intravenously infused LPS into growing calves and demonstrated a greater than tenfold increase in circulating insulin (152). Again, the increase in insulin in both models is energetically difficult to explain, as feed intake was severely depressed in both experiments.

The mechanisms by which LPS increases insulin secretion are unknown but may be mediated by LPS-induced proinflammatory cytokines. Two lines of evidence support this. First, the mammary-infused LPS (151) was probably sequestered within the gland and likely did not enter systemic circulation. Second, the timing of the increase in insulin in both models (151, 152) was approximately 2 h postinfusion, which implies that a secondary messenger caused the increased insulin secretion. Interestingly, in the intravenous LPS-infusion experiment, insulin concentrations were not different at 1 h but were increased more than tenfold at 2 h post–LPS infusion. Insulin levels rapidly decreased and were at pre–LPS infusion levels at 4 h post–LPS infusion. The data above indicate that insulin must be involved with some type of signaling cascade that either initiates infection-induced pyrexia (153), stimulates immune cell activation, or provides a protection signal that allows systemic tissue to withstand the upcoming inflammatory response (154). One such protection signal may be insulin's role in activating HSPs, which are induced in a variety of cells during acute infection (148).

As mentioned above, the diabetes literature suggests that therapeutic hyperthermia can improve insulin sensitivity. For example, humans have improved glucose disposal the day after spa/sauna treatment (129), a finding confirmed in rodent models (127). Exercise-induced improved insulin signaling may be partly mediated simply by an exercise-induced increase in body temperature (129). The effects of HS on farm-animal insulin sensitivity (with regards to glucose uptake) are not clear and may depend upon the magnitude and duration of animal exposure to hyperthermia. For example, we have demonstrated that heat-stressed lactating cows disposed of a glucose load quicker than did pair-fed thermal neutral controls (29). Using the hyperinsulinemic-euglycemic clamp technique, we also demonstrated that insulin sensitivity is improved in growing heat-stressed calves (152), and we tentatively confirmed this in lactating cows (155). Interpreting hyperinsulinemic-euglycemic clamp results for lactating dairy cows is difficult because the heat-stressed cows were hypoglycemic compared with the thermal-neutral cows at the start of the clamp. Overall, the quantity of glucose infused to maintain euglycemia was similar between the heat-stressed and thermal-neutral cows, but evaluating the rate of glucose infusion/basal glucose indicates that HS cows required more glucose (18%) to maintain euglycemia (155).

The effects of HS on insulin-induced glucose uptake remain ambiguous because we could not replicate the increased glucose disposal following a glucose tolerance test in another lactating dairy cow trial (30) or in a growing calf trial (118). Reasons for the inconsistencies are not clear but may involve effective intracellular insulin signal transduction. We conducted a study designed to examine the acute insulin responsiveness of skeletal muscle during an insulin tolerance test by measuring insulin receptor and AKT abundance as well as AKT phosphorylation (156). Both HS and pair feeding impaired glucose-disposal rates similarly compared with ad libitum thermal-neutral conditions. Protein abundance of the insulin receptor, insulin receptor substrate, and AKT remained stable between periods and environments. Insulin increased phosphorylated AKT in each period; however, this response tended to decline in pair-fed animals but not during HS. These results indicate that mild insulin resistance may develop during HS in a manner related to reduced nutrient intake. Moreover, a reduction in insulin responsiveness of skeletal muscle may stem from a postreceptor signaling defect (156). How HS alters insulin responsiveness depends upon a variety of variables and likely occurs in a tissue-specific manner. What is consistent among these studies is that heat-stressed animals have a much larger insulin response to insulin secretagogues (discussed above). The increased insulin response, coupled with a similar rate of glucose disposal, actually indicates a state of insulin resistance. Insulin resistance also occurs during malignant hyperthermia and is thought to result from elevated intracellular Ca^{+} (157).

Glucose uptake is not mediated only by insulin, as there are several non-insulin-dependent glucose transporters (GLUTs) that are tissue specific and have different affinities for glucose (158). Heat stress has been shown to increase in vitro GLUT1 (159) and SGLT-1 (160). Heat stress may alter multiple routes of glucose uptake, and this is likely tissue specific; therefore, obtaining an accurate understanding of how HS alters insulin-dependent and -independent glucose disposal is challenging.

INTRACELLULAR ENERGETICS

Studies investigating the effects of HS on cellular metabolism in passively induced hyperthermia can provide conflicting information based on model variations involving differences in magnitude and duration of hyperthermia, species, or cell type (see Literature Variation section below). For example, Dickson & Calderwood (161) observed decreased in vitro rates of anaerobic glycolysis at 42°C, but in vivo, whole-body hyperthermia increased glucose metabolism. An increase in energy demand caused by elevated temperatures is met by increasing ATP synthesis, which has been demonstrated in hyperthermic cells by measuring the incorporation of 3H-adenosine into ATP (162). However, the metabolic changes that occur as a result of thermal insult may lead to a depletion in energy reserves, possibly owing to altered regulation of key metabolic points such as the pyruvate dehydrogenase (PDH) complex (94).

Owing to the contribution of skeletal muscle to overall animal mass and the fact that it is an energetically expensive tissue to maintain, small changes in its fuel efficiency can have large impacts on feed conversion and nutrient flux. The PDH complex controls glucose flux through the TCA cycle and is responsible for the irreversible conversion of pyruvate to acetyl-CoA. The PDH complex is regulated primarily via covalent modification by pyruvate dehydrogenase kinases (PDKs), which inactivate PDH, and pyruvate dehydrogenase phosphatases (PDPs), which activate PDH (163). The activities of the PDK and PDP are themselves regulated at the transcriptional level by intracellular energy status, metabolism intermediates (acetyl-CoA and NADH), transcription factors, and hormones such as cortisol and insulin (164). Furthermore, LPS (derived from the heat-stressed gastrointestinal tract; see above) inhibits muscle PDH via two pathways: directly, via TNFα production, and indirectly, via the NFKB, AKT1, and FOXO pathways (165). Cellular energy status (i.e., the ATP-to-AMP ratio) is one of the primary mechanisms for determining substrate utilization. Inactivation the PDH complex may be a glucose-sparing mechanism, although reduced oxidative glucose metabolism during HS may instead be the result of events stemming from intracellular reactive oxygen species (ROS). An attractive candidate known to shift cellular metabolism toward glycolysis is hypoxia-inducible factor (HIF) (166). Reports indicate that HIF acts as a metabolic switch for cellular adaptation to hypoxia by increasing PDK expression and downregulating mitochondrial oxygen consumption (167). Although much research on HIF signaling has focused on oxygen tension, there is growing understanding that HIF is regulated by stresses such as hyperthermia and ROS (168, 169). Our preliminary experiments demonstrated a fivefold increase in HIF-driven transcriptional activity during HS in primary myocytes (R.P. Rhoads & L.H. Baumgard, unpublished observations). Consistent with a potential shift in cellular metabolism away from carbohydrate oxidation, we observed increased skeletal-muscle PDK4 mRNA abundance in rodents, pigs, and ruminants during HS (89, 98, 99, 170). We have also demonstrated that exposing rats to an acute (6-h) heat load markedly induces hyperthermia, increases HSP70 mRNA abundance, and alters the expression of many enzymes associated with energy metabolism in a tissue-specific manner (89). For example, within the tibialis anterior, a predominantly glycolytic skeletal muscle, lactate dehydrogenase A (LDHa) mRNA abundance was increased, whereas expression of LDH isoforms in the soleus, a predominantly oxidative muscle type, was not different between thermal-neutral and HS conditions. This indicates an increase in lactate production capacity by type II but not type I skeletal muscle in response to a heat load. Further examination of carbohydrate oxidation capacity demonstrated that levels of skeletal-muscle PDH protein abundance did not differ between environments; however, levels of phosphorylated (inactive) PDH were increased by exposure to single and multiple heat loads (89). This suggests a decrease in glucose oxidative capacity, which corresponds to the heat-induced increase in PDK4 mRNA abundance we observe in multiple species (see above). Our data also agree with a study utilizing heated melanoma cells in which ratios of lactate/pyruvate and $NADH/NAD^+$ were increased, which indicates that pyruvate entry into the TCA cycle (via PDH) may be impaired with HS (93). Moreover, such changes appear to be consistent with impaired cellular energy status, perhaps owing to mitochondrial dysfunction possibly related to muscle-fiber type during hyperthermia. Taken together, increased transcription of PDK4, and the subsequent inactivation of the PDH complex, might serve as a mechanism to reduce substrate oxidation and mitochondria ROS production in an effort to prevent cellular damage during HS.

Previous reports suggest that mitochondria may be affected directly by HS (171, 172). Histological analysis of skeletal muscle in a rat heat stroke model showed that mitochondrial abnormalities, denoted as ragged red fibers and electron-microscopic observations, revealed an increased number and size as well as altered morphology of mitochondria (173, 174). Interestingly, the location of mitochondria from heat-stressed rats was also altered, because skeletal muscle expressing ragged red fibers exhibited mitochondria aggregated within the subsarcolemmal space, which suggests an increased energy demand of the plasma membrane owing to hyperthermia (173). In rat cardiomyocytes, HS resulted in swollen mitochondria with broken cristae and low matrix density, in addition to decreased ATP content in the myocardium (175, 176). Because mitochondria are a major source of energy production, mitochondrial damage can impair a cell's ability to compensate for the increased energy demands (177) imposed by environmental stresses, and it may contribute to increased levels of oxidative stress.

GLUCOSE SPARING

Blood lactate levels are consistently elevated in many heat-stressed models (93, 102), including cattle (104). The origin of this lactate is currently unknown but may include the gastrointestinal tract and muscle. Presumably the liver would clear the mesentery-derived lactate (178), so it is unlikely that splanchnic tissue is the source. Skeletal muscle is a likely candidate simply because of its sheer mass, but actual blood flow to the muscle tissue during HS increases (105), and therefore anaerobic glycolysis theoretically should not be necessary. However, because HS upregulates PDK4 and hyperphosphorylation of PDH reduces pyruvate entry into the TCA cycle (163; see above), an increase in LDH allows for the increased mass-action conversion of pyruvate into lactate. Pyruvate is also the precursor to alanine via alanine aminotransferase (179), and circulating concentrations of this amino acid and enzyme increase in a variety of heat-stressed animals (102, 180). Consequently, it appears that pyruvate entry into the TCA cycle is a bottleneck, which thus increases pyruvate-derived metabolite production. Heat-induced hyperlactemia may also contribute to the altered postabsorptive carbohydrate and lipid metabolism described above. Lactate binds to adipocyte G-protein receptors and reduces lipolysis, decreasing circulating NEFA concentrations (181). Further, lactate metabolism results in a downregulation of CPT-1 and thus reduces NEFA entry into the mitochondria (181).

The accelerated aerobic glycolysis that occurs in skeletal muscle during HS resembles the Warburg Effect, the system used by most cancerous cells to generate ATP (182). The evolutionary rational and energetic reasons underpinning such a strategy during HS are not clear. For example, glycolysis is much less energetically efficient (net: 2 ATP) than is complete oxidative phosphorylation (36–38 ATP) (179). We originally thought that lactate leaving the muscle during HS was converted back into glucose via the Cori cycle (183). However, in nonruminants only a small percentage of lactate is recycled via the Cori cycle, and most of it is actually taken up by extrahepatic tissues, converted back into pyruvate, and then oxidized in the TCA cycle (184); this presumably is the case in cattle as well. The increased reliance on lactate for energy in tissues capable of oxidizing lactate may be a glucose-sparing mechanism employed to ensure adequate glucose availability for cells that are obligate glucose users. This process is similar to the systems described in hyper-immune-activated animals (185). Cells that rely primarily on glucose for energy are the central nervous system, red blood cells, and cells composing the immune system (156, 179). Normally during periods of inadequate nutrient intake, the central nervous system would have access to NEFA-derived ketones. However, we and others have clearly demonstrated that heat-stressed animals appear metabolically inflexible and thus have limited access to either NEFA or ketones. Therefore, the altered lactate metabolism may be a strategy to ensure glucose delivery to the brain and red blood cells. In addition, immune cells also primarily oxidize glucose (and glutamine) for energy, which leads to the notion that hypoglycemia during endotoxemia is caused by increased glucose utilization by macrophage-rich tissues (186). As already mentioned, heat-stressed animals have a leaky gut, and the mesenteric-derived LPS likely cause a local inflammatory response (149). If the intestinal barrier function is severely compromised, the liver may be overwhelmed and unable to remove all LPS. As a consequence, LPS would enter the systemic circulation and elicit a whole-body inflammatory response (149). In severely septic human patients, energy expenditure increases by approximately 50% (187); extrapolated to heat-stressed lactating cows, this would represent approximately 4 Mcal of increased maintenance costs. If this increased energy need were met via aerobic glycolysis (185), it would require approximately 1,000 g glucose per day. Even if overestimated by 50–75%, the increased glucose requirement would be 250–500 g, which is remarkably similar to the glucose shortage we report during HS (see above). Therefore, we believe that the altered lactate metabolism maybe a glucose-sparing mechanism to ensure that the central nervous system and immune cells have an adequate fuel supply. From a lactation and growth standpoint, this change in the hierarchy of fuel utilization decreases glucose partitioning to the mammary gland and skeletal muscle.

COORDINATED METABOLIC CONSEQUENCES OF HEAT STRESS

Insulin is a potent regulator of both carbohydrate and lipid metabolism and may play an important role in mediating HS regulation of postabsorptive nutrient partitioning (**Figure 5**). Insulin stimulates glucose uptake via glucose transporter type 4 in responsive tissues (e.g., muscle and adipose tissue) and is likely responsible for the heat-induced hypoglycemia frequently reported in

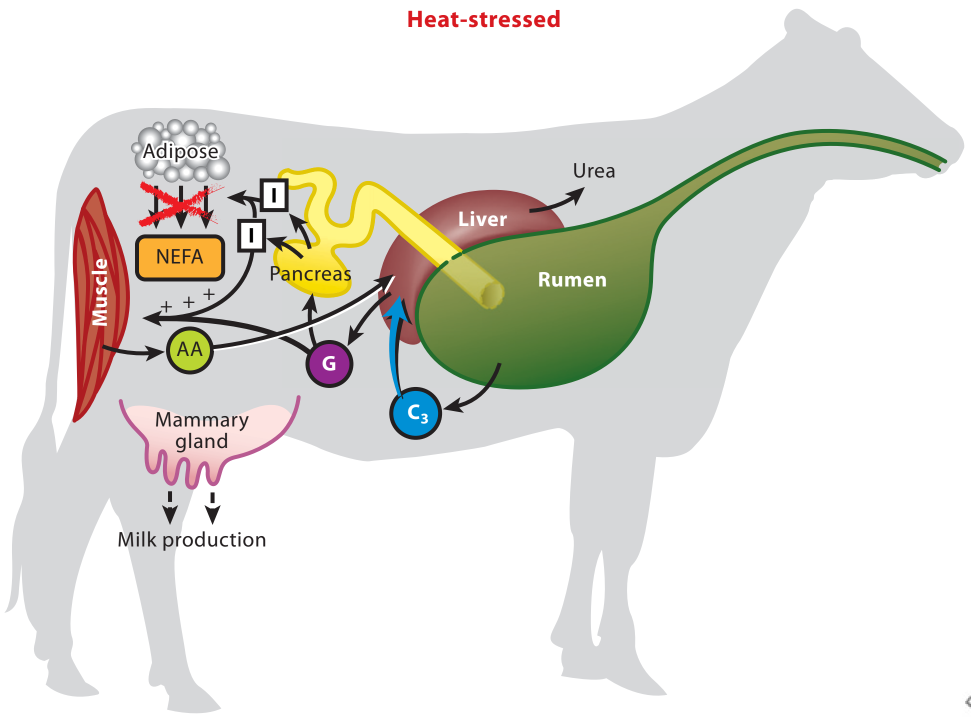

Figure 5

Nutrient partitioning in a heat-stressed lactating cow fed ad libitum. Compared with that of a thermal neutral cow on a restricted plane of nutrition (**Figure 2**), the pancreas secretes more insulin, which seemingly prevents the cow from sparing glucose for the synthesis of milk. The heat-stressed cow enters a metabolically inflexible state, which is characterized primarily by minimal use of body fat reserves. Abbreviations: AA, amino acids; C_3, propionate; E, energy; G, glucose; I, insulin; NEFA, nonesterified fatty acid.

multiple chronic HS models (29, 94, 118–120, 189). This occurs despite an increase in intestinal glucose absorptive capacity (70) and enhanced renal glucose reabsorptive ability (190).

Insulin is also a potent antilipolytic hormone (85), and this may explain why heat-stressed animals do not mobilize adipose tissue triglycerides. Limiting adipose tissue mobilization is the key step by which heat-stressed animals are prevented from employing glucose-sparing mechanisms normally enlisted to maintain milk production (**Figure 5**) or skeletal muscle accretion during periods of temporary malnutrition. The lack of available NEFA to systemic tissues for oxidative purposes is coupled with reduced volatile fatty acid (primarily acetate because of decreased feed intake in ruminants) availability, and thus both glucose and amino acid oxidation may increase. The efficiency of capturing ATP from amino acid oxidation is low (meaning metabolic heat production is high) (179), so it is an unlikely fuel choice during hyperthermia. Therefore, glucose apparently becomes a favored fuel for heat-stressed animals (93), which is consistent with the increase in respiratory quotient observed in hyperthermic humans (96).

The increase in skeletal-muscle protein catabolism (mentioned above) is peculiar given insulin's role in stimulating protein synthesis and preventing proteolysis (191). Heat stress is thought to increase membrane permeability, allowing for cytosolic Ca^{+} leakage, which may increase protein sensitivity to HS (192). We believe that breaking down skeletal muscle is likely a strategy to supply precursors for gluconeogenesis, consistent with data from Rhoads et al. (101), and acute phase proteins rather than to supply oxidative substrates (because of the inefficiency in capturing ATP from amino acid–derived substrates).

CONCLUSIONS

The heat-stressed animal initiates a variety of postabsorptive metabolic changes that are largely independent of reduced feed intake and whole-animal energy balance. These changes in nutrient partitioning seemingly are adaptive mechanisms employed to prioritize the maintenance of euthermia. The primary difference between a thermal-neutral and a heat-stressed animal in a similar energetic state is the inability of the hyperthermic beast to employ glucose-sparing mechanisms to homeorhetically prioritize product (milk and meat) synthesis. From an animal agriculture standpoint, these survival strategies reduce productivity and seriously jeopardize farm economics. Defining the biology and mechanisms of how HS threatens animal health and performance is critical in developing approaches to ameliorate current production issues and is a prerequisite for generating future mitigating strategies to improve animal well-being, performance, and agriculture economics.

SUMMARY POINTS

1. Heat stress is a global problem that threatens the ability to produce sufficient animal protein for human consumption.
2. Distinct indirect (mediated by decreased nutrient intake) and direct effects of heat stress are responsible for reduced animal productivity during the warm summer months.
3. Heat stress directly affects multiple systems, and the summation of these altered physiological systems contributes to reduced animal productivity.
4. Heat stress compromises the ability of the intestinal track to maintain an effective barrier to luminal toxins.
5. From a metabolism perspective, the inability to mobilize adipose tissue during heat stress prevents a cascade of events that would normally spare glucose for agriculturally

productive purposes. We refer to this altered postabsorptive state as "metabolically inflexible."

FUTURE ISSUES

1. Identifying what is responsible for increased insulin concentration and function during heat stress will likely provide insight on future mitigation strategies.
2. A better understanding of altered whole-animal and tissue-specific insulin sensitivity by various levels of heat stress (the severity, magnitude, and duration) is needed in the field.
3. Understanding the coordinated response to heat-induced intestinal permeability via interaction between the immune system and nutrient partitioning is necessary.
4. Characterizing the mechanisms of how, when, and why the heat-stressed animal initiates aerobic glycolysis is important.
5. Ideal genetic selection criteria should focus on animal performance by identifying the combination of genes responsible for improved thermal tolerance with genes that maintain or enhance production.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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