Nutritional Interventions to Alleviate the Negative Consequences of Heat Stress$^1,2$

Robert P. Rhoads,3* Lance H. Baumgard,4 Jessica K. Suagee,3 and Sara R. Sanders5

3Department of Animal and Poultry Sciences, Virginia Tech, Blacksburg, VA; 4Department of Animal Science, Iowa State University, Ames, IA; 5Department of Animal Sciences, University of Arizona, Tucson, AZ

ABSTRACT

Energy metabolism is a highly coordinated process, and preferred fuel(s) differ among tissues. The hierarchy of substrate use can be affected by physiological status and environmental factors including high ambient temperature. Unabated heat eventually overwheels homeothermic mechanisms resulting in heat stress, which compromises animal health, farm animal production, and human performance. Various aspects of heat stress physiology have been extensively studied, yet a clear understanding of the metabolic changes occurring at the cellular, tissue, and whole-body levels in response to an environmental heat load remains ill-defined. For reasons not yet clarified, circulating nonesterified fatty acid levels are reduced during heat stress, even in the presence of elevated stress hormones (epinephrine, glucagon, and cortisol), and heat-stressed animals often have a blunted lipolytic response to catabolic signals. Either directly because of or in coordination with this, animals experiencing environmental hyperthermia exhibit a shift toward carbohydrate use. These metabolic alterations occur coincident with increased circulating basal and stimulated plasma insulin concentrations. Limited data indicate that proper insulin action is necessary to effectively mount a response to heat stress and minimize heat-induced damage. Consistent with this idea, nutritional interventions targeting increased insulin action may improve tolerance and productivity during heat stress. Further research is warranted to uncover the effects of heat on parameters associated with energy metabolism so that more appropriate and effective treatment methodologies can be designed. Adv. Nutr. 4: 267–276, 2013.

Introduction

Summer temperatures have been increasing worldwide, and some predict this trend will continue (1,2). Average mean temperatures in North America are projected to increase 1.8 C to 4 C during this century (1). Regions of the United States that typically experience heat waves are expected to have a dramatic increase in the magnitude of these summer events. For example, in California, the number of heat wave days is expected to double and the “heat wave season” to lengthen an estimated 20% (3). As heat waves become more frequent and longer in duration, heat-related morbidity and/or mortality are also likely to increase (4,5).

Heat claims the lives of more Americans annually than hurricanes, lightning, tornadoes, and floods combined (6). An estimated 1500 heat-related deaths are reported each summer (7), and the CDC (8) suggests that this is underestimated by at least 50%. Heat waves in Chicago during 1995 (9,10) and 1999 (11) claimed ≥600 and nearly 100 lives, respectively. Worldwide, the numbers are even more staggering. In a 2003 heat wave that lasted ~2 wk, an estimated 50,000 Europeans died (12,13), 15,000 of those in France alone (14,15). Increased body temperature disturbs biological systems, and this ranges from heat edema to heat stroke [heat stroke being the least common but most severe (16)]. The onset of heat-related illnesses can arise due to exposure to increased ambient temperatures (classic heat stress) or as a result of exercise [exertional heat stress (17)]. Diagnosing heat-related illness can be difficult because symptoms vary depending on the extent and magnitude of exposure and great individual variability to similar heat loads (18). Although many aspects of heat stress have been extensively researched, relatively little is known about the metabolic and biochemical changes that occur during heat exposure. In particular, it is unknown why certain populations are less tolerant to heat than others. Diabetic individuals, for example, have a higher risk of experiencing a heat-related illness than those who are non-diabetic (19), and death rates among those with diabetes increases significantly.
during the summer months (20). A review by Schuman (21) noted that during heat waves, diabetic individuals had the greatest increase (of all major chronic diseases) in death rates, although the reason for this increased susceptibility remains ill-defined.

In agriculturally relevant species, heat stress negatively affects many production parameters including milk yield and composition, growth, reproduction, and carcass traits. In addition, a heat load increases health care costs, and, depending on the severity, animals can die of severe thermal stress (especially lactating cows and animals without shade). A 2006 California heat wave purportedly resulted in the death of >30,000 dairy cows (22), and a recent heat wave in Iowa killed at least 4000 head of beef cattle (23). Furthermore, almost 50% of Canadian summer days are considered environmentally stressful to dairy cows (24). This illustrates that many geographic locales, including temperate and northern climates, can be susceptible to extreme and lethal heat. Therefore, environmental heat stress is an animal welfare issue and a financial burden to agri-industries (~$900 million/y for dairy and >$300 million/y in beef and swine in the US alone (25,26)). Improvements in farming infrastructure [i.e., cooling systems, barn construction (27,28)] have alleviated some negative effects of thermal stress on animal agriculture, but production still decreases during the summer. Consequently, heat stress is one of the costliest issues facing progressive animal producers and certainly one of the primary constraints to efficient and profitable animal agriculture in developing countries (29).

**Current status of knowledge**

**Cellular heat stress response**

Exposure to increased ambient temperatures can result in significant alterations and damage at the cellular level. Many intracellular molecular structures rely on a variety of relatively weak interactions for stabilization, and these interactions are easily disrupted by changes in the microenvironment [i.e., increases or decreases in temperature and pH (30)]. Heat can negatively affect cell components directly, such as unfolding and subsequent aggregation of proteins (31–33). Protein synthesis appears to be particularly impaired by heat. For example, Mondovi et al. (34) and Henle and Leeper (35) noted that DNA, RNA, and protein synthesis was rapidly inhibited by heat treatment, with the reduction being greatest for protein synthesis followed by DNA and finally RNA synthesis (34,35). Furthermore, reductions in protein, DNA, and RNA synthesis after heat exposure can be rapid and occur within 10 min at 42 C in HeLa and CHO (Chinese hamster ovary) cells (36). Protein synthesis is affected to the greatest extent but recovers the most quickly, whereas resumption of DNA synthesis requires an extended period of time (35).

The cellular response to a heat load includes activation of transcription factors such as heat shock factors (HSFs) (37–39), expression of proteins associated with acute homeostatic response such as heat shock proteins (HSPs), and altered gene expression [reviewed by Collier et al. (40)]. This coordinated response leads to changes in the expression of proteins necessary for restoring cellular function and directing cellular remodeling, such as regulatory proteins, cell-cycle control proteins, and structural proteins, as well as those determining cell fate, including proteins involved in apoptotic and antiapoptotic pathways (37–39,41). Although multiple HSF isoforms exist, HSF1 is the central transcription factor involved in the heat shock response (42,43) because mice lacking HSF1 are unable to mount a heat shock defense (44). HSF1 is activated in response to various stressors, including heat, oxidative stress, and non-native protein synthesis (45–47). HSF2 is primarily transcribed in response to inhibition of proteasome activity and thus complements the response of HSF1 to an increase in misfolded proteins (48).

**Heat shock proteins.** Of particular importance to cell survival during hyperthermia are HSPs. Members of this protein family are ubiquitously expressed across species and are present at low levels in cells under normal conditions, but their levels increase greatly, but transiently, on a cellular insult (49–52). Classically known as molecular chaperones, HSPs bind to unfolded or misfolded proteins and help restore their native conformation (53–55). HSPs are grouped based on their molecular weight and amino acid sequence (56,57) as well as by structure and function (58). Major HSPs in mammalian cells include HSP110, 90, 70, 60, and 27 (59), each having separate functions and cellular locations (56). Of these, HSP70 plays a heightened role in cryoprotection (60) and is frequently used as a biomarker of cellular stress. Expression levels of HSP70 are most closely indicative of the magnitude and duration of thermal stress (61). Ultimately, if damage from heat exposure is not/cannot be repaired (such as that caused by mitotic catastrophe), cell death via heat-induced apoptosis will occur (33). Intriguing work indicates that circulating HSP70 concentrations also increase during heat stress (62,63), demonstrating a need to further investigate the origins and functions of extracellular HSP70.

In addition to their role in protecting cells from heat-induced protein misfolding, HSPs may enhance insulin function. Obesity increases activation of stress kinases, which then increase serine phosphorylation of the insulin receptor substrate 1 (IRS-1), and this ultimately reduces the functionality of the insulin signaling pathway (64–66). Expression of HSPs is reduced in obese patients, and heat therapy (e.g., saunas, spas) improves insulin function due to the ability of HSPs to reduce serine phosphorylation of IRS-1 through reducing stress kinase activation (67,68). Taking this further, pharmacologically inducing HSP70 improves insulin sensitivity (62). Together, these studies demonstrate that HSPs are important for proper insulin function and suggest that strategically manipulating the insulin-HSP axis may improve human and animal health and productivity during heat stress.
**Reactive oxygen species.** Heat stress likely increases and/or induces oxidative stress, possibly leading to mitochondrial damage, which is the primary intracellular source of reactive oxygen species (ROS). Damaged or malfunctioning mitochondria, due to the effects of heat directly or by increased oxidative stress, may be a contributing factor to alterations in metabolism during heat stress. It is widely accepted that mitochondrial respiration is the primary source of ROS (69,70), with 0.2% of oxygen consumed converted to superoxide in the normal state (71). Levels of ROS are determined by production and ROS degradation rates and/or inactivation, and an appropriate balance is important for maintaining cellular homeostasis (72). Generation of ROS, such as superoxide, can damage proteins, DNA, and lipids (73,74) and decrease mitochondrial function (75). Such oxidative damage results when a cell accumulates excessive amounts of ROS, a condition that occurs when ROS production exceeds cellular defenses. Detoxifying ROS occurs by several nonenzymatic antioxidants, including ascorbic acid and glutathione, in addition to ROS-scavenging enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and peroxiredoxin (76–78). Antioxidants are maintained at relatively low levels, but increase quickly and dramatically in response to increased ROS production. Cooperation among enzymes is common in ROS detoxification. For example, superoxide dismutase converts superoxide radicals into hydrogen peroxide and oxygen; catalase and peroxidases then convert the hydrogen peroxide to water (79,80).

Heat stress increases ROS production, and there are many similarities in the pattern of gene expression of heat-stressed and oxidative-stressed cells (81,82). Levels of ROS-scavenging enzymes were increased (transcript and protein levels) by heat stress (83–85). Rat intestinal epithelial cells exposed to severe and acute heat stress had increased ROS flux (86), and increased superoxide formation was detected in heat-stressed mouse diaphragm muscle (87). Studies by Mujahid et al. (88,89) revealed an increase in mitochondrial superoxide generation and oxidative damage to mitochondrial proteins and lipids in the skeletal muscle of heat-stressed chickens. Similarly, heat stress causes oxidative stress in transition dairy cows (90). Acute heat-stressed broiler chickens had a 2-fold increase in malondialdehyde, a marker of lipid peroxidation, in skeletal muscle (91). In mitochondria of rat cardiomyocytes, oxidative metabolism was reduced, thereby significantly depleting ATP content (92) and uncoupling of oxidative phosphorylation leading to an increase in ROS production and oxidative stress. Superoxide production can be reduced by uncoupling of the electric transport chain by uncoupling proteins or adenine nucleotide translocator, however, in heat stress conditions, uncoupling proteins are downregulated (89), which is probably a protective mechanism to prevent further heat production. ROS are produced during normal aerobic metabolism; therefore, the increased energy demands imposed by elevated ambient temperatures may also contribute to ROS generation and oxidative stress.

**Systemic heat stress response**

The physiological basis by which heat stress affects production and performance in farm animals includes contributions from reduced feed intake, an altered endocrine status, metabolic shifts at the systemic and cellular levels, and changes in body composition. For information about the impact of heat stress on nutrient intake and the endocrine profile, the reader is referred to reviews by Collier et al. (93), West (94), and Bernabucci et al. (95). Here, the focus centers on heat-induced postabsorptive metabolic alterations.

Production and observational data suggest that heat stress may alter metabolism differently than would be expected based on calculated whole-body energy balance. For example, heat-stressed sows (96) and heifers (97) do not lose as much body weight and body condition, respectively, as do their pair-fed thermoneutral counterparts. In addition, pigs reared in heat-stress conditions have reduced muscle mass and increased adipose tissue, and this has been documented frequently in the past 40 y (98,99). This phenomenon is not unique to pigs because heat stress also alters carcass composition similarly in rodents (100,101) and growing poultry (102–105). It is counterintuitive that heat stress causes a decrease in nutrient intake and depresses growth but increases carcass lipid accretion and decreases carcass nitrogen content. In thermoneutral conditions, animals consuming a restricted diet will deposit protein at the expense of lipid accretion (i.e., the carcass lipid-to-protein ratio decreases, meaning that the carcass becomes leaner) and the quantity of lipid deposited per unit of energy consumed decreases (106–108). Hence, the reduced feed intake–to–body composition relationship is exactly the opposite in animals reared in heat-stress conditions compared with thermoneutral animals and is independent of the plane of nutrition.

We recently demonstrated that despite reduced feed intake and loss of body weight, heat-stressed cows and pigs do not have an increase in plasma nonesterified fatty acids (NEFAs) (109–111), and this agrees with other heat-stress models (97,112,113). The lack of an elevated NEFA response to body weight loss is especially surprising because acute heat stress causes a marked increase in circulating cortisol, norepinephrine and epinephrine levels (93), catabolic signals that normally stimulate lipolysis, and adipose mobilization. This is also surprising because calculated energy balance is traditionally thought to be closely associated with circulating NEFA levels (114). Furthermore, we recently demonstrated that heat-stressed cows have a blunted (compared with pair-fed thermoneutral controls) NEFA response to an epinephrine challenge (115). These observations agree with rodent results indicating that heat stress reduces in vivo lipolytic rates and in vitro lipolytic enzyme activity (116). The fact that heat-stressed animals fail to enlist this “shift” in postabsorptive energetic metabolism (despite inadequate nutrient intake) may indicate that heat stress directly (not mediated by feed intake) affects fuel selection and overall energetics.
The aforementioned changes in lipid metabolism variables may be the result of increased insulin levels and/or enhanced insulin sensitivity because insulin is a potent lipogenic and antilipolytic hormone (117). In fact, despite the marked reductions in dry matter intake, heat stress increases insulin sensitivity in rodents [see review by DeSouza and Meier (118)], and basal insulin levels in rodents (116), heat-stressed pigs (111), a malignant hyperthermia porcine model (119), growing steers (120), and lactating cows (121,122). In addition, heat-stressed sheep (123), growing cattle (120), and lactating cows (122) have an increased insulin response to a glucose tolerance test (Fig. 1). The increase in circulating insulin levels appears due to increased pancreas secretion rather than reduced circulating insulin removal because of the acute marked difference in insulin levels between heat-stressed and thermoneutral pair-fed animals after administration of an insulin secretagogue (29).

Due to the apparent lack of NEFA availability as a fuel substrate, it appears that heat-stressed animals increase both their production of, and reliance on, glucose as a fuel. For example, heat-stressed human athletes have increased endogenous glucose production and whole-body enhanced carbohydrate oxidation at the expense of lipids (124–126). In addition, endogenous glucose production typically decreases after ingesting carbohydrates, but exogenous sugars are unable to blunt the heat stress–induced liver glucose output (127). The increased hepatic glucose output during heat stress originates from both increased glycogenolysis (125) and increased gluconeogenesis (128). The increased liver glucose output during heat stress may in part be mediated by upregulated hepatic pyruvate carboxylase gene expression, a rate-limiting enzyme controlling lactate and alanine entry into the gluconeogenic pathway (129–131). This is supported by flux data indicating that lactate’s contribution to gluconeogenesis increases in hyperthermic rodents (128). Furthermore, heat-stressed chicks have increased intestinal sodium-dependent glucose transporter 1 activity and thus glucose absorption (132). Cell culture experiments demonstrate heat-induced activation of a high-affinity sodium-dependent glucose transporter and enhancement of sodium-glucose cotransport capacity during a thermal load (133,134). We have also demonstrated that a larger percentage of hepatically derived glucose is used for non–milk-synthesizing purposes in heat-stressed cows, and this suggests an increase in glucose use as a fuel (115). Further, we have shown using stable isotopes that whole-body (presumed to be primarily from hepatic tissue) glucose production and the glucose response to an epinephrine challenge (used as a proxy for hepatic glycoigenolytic sensitivity) does not differ between heat-stressed and pair-fed thermoneutral controls (115) despite reports suggesting that the liver becomes partially dysfunctional during heat stress (135,136). Collectively, evidence from a variety of species suggests that hepatic carbohydrate metabolism is not compromised by heat stress, and presumably many of these changes occur to maximize glucose availability when the metabolic option of using adipose tissue–derived energy has been prevented.

Skeletal muscle is mobilized during periods of inadequate nutrient intake (in thermoneutral conditions) or because of muscular damage and/or disease. We have demonstrated that heat-stressed pigs (111), cows (110), and heifers (97) have increased plasma urea nitrogen levels compared with thermoneutral controls. Plasma urea nitrogen can sometimes be difficult to interpret because it originates from at least 2 sources (depending on species): inefficient rumen ammonia incorporation into microbial proteins or from hepatic deamination of amino acids mobilized from skeletal muscle. A better circulating indicator of muscle catabolism is either 3-methyl-histidine or creatine, both of which are increased in heat-stressed poultry (103), rabbits (137), pigs (111), and lactating cows (138). Additional evidence indicating that heat stress directly affects protein metabolism is decreased milk protein levels from heat-stressed cows (109,110), and it appears that α and β casein synthesis is most susceptible (139). The reduction in muscle and mammary protein synthesis during heat stress is perplexing because an elevation in plasma insulin, typically observed during heat stress (Fig. 1), would reduce proteolysis and stimulate tissue protein synthesis (assuming adequate amino acid supply) during normal physiological states.

Although the reasons for increased insulin action and circulating concentrations during heat stress remain unclear, the increase in insulin is critical for its role in activating the cellular stress response (140). In addition to altered plasma insulin levels, heat stress markedly increases the insulin receptor expression in pig reproductive tissues (141).

![Figure 1](https://academic.oup.com/advances/article-abstract/4/3/267/4591580/22-January-2019)
As stated previously, diabetic humans are more susceptible to heat-related illness and death (9,21). Similarly, diabetic rats have an increased mortality rate when exposed to severe heat, and exogenous insulin increases their survival time (142). Furthermore, nonlethal heat stress ameliorates proxies of insulin insensitivity in diabetic rodents (143,144) or rodents fed high-fat diets (145). This is similar to reports indicating that thermal therapy (saunas and hot baths) improves insulin sensitivity in humans (146). Insulin’s role in thermal stress adaptation appears to be an ancient mechanism preserved during evolution as even heat-stressed simple eukaryotes increase both insulin synthesis and insulin binding (147). Regardless of why, heat stress is one of the very few nondiabetic models of which we are aware in which nutrient intake is markedly reduced, but basal and stimulated insulin levels are increased. Hence, there is growing evidence to suggest that insulin action is a key component of the heat-stress response, and this may explain the observed phenotypic changes (increased carcass lipid) in farm animals during the summer.

**Nutritional supplementation during heat stress**

Because of the obvious health implications to humans and farm animals, there is a growing interest in strategically altering the diet in an attempt to improve the response to heat stress. A thorough description of agricultural dietary strategies is not within the scope of this article, and the reader is referred to other reviews (148–151). This section concentrates on dietary manipulation of systemic insulin sensitivity because it is clear that proper insulin action is one of the key components of successfully adapting to and surviving a heat load. Therefore, supplementing diet ingredients or pharmaceuticals that enhance insulin sensitivity may be an effective tactic to improve the likelihood of surviving an otherwise lethal heat load.

**Lipoic acid.** Lipoic acid is synthesized from octanoic acid by the mitochondria (152–154), and it serves as a cofactor of mitochondrial enzymes that perform oxidative decarboxylation (155). Lipoic acid and its reduced form, dihydrolipoic acid, scavenge ROS and nitrogen species (156,157) and enhance cellular glucose uptake due to their insulin mimetic action (158). Oral lipoic acid supplementation in poultry decreased plasma glucose and increased whole-body insulin sensitivity while increasing plasma triglycerides and adipose tissue lipolysis (159,160). However, the effectiveness of lipoic acid supplementation to alter glucose availability may be dependent on the magnitude and duration of heat-stress events (161). Similar to chickens, oral lipoic acid supplementation reduced plasma glucose concentrations in young swine maintained in thermoneutral conditions (162). It appears that lipoic acid enhances insulin action in thermoneutral animals, and, thus, the ability of lipoic acid to promote thermal tolerance during chronic heat-stress conditions is of obvious interest. In horses, lipoic acid supplementation reduces blood lactate concentrations during exercise and increases citrate synthase activity before and after exercise (163), indicating that lipoic acid enhances oxidative metabolism. In addition, lipoic acid supplementation reduced exercise-induced increases in plasma amino aspartate transferase and creatine kinase, indicating that it may reduce muscle damage (164). Thus, dietary supplementation with either lipoic or dihydrolipoic acid may improve heat tolerance and animal performance during heat stress by enhancing insulin action.

**Chromium.** Chromium is a micronutrient that facilitates insulin action on glucose, lipid, and protein metabolism (165). Little is known about actual dietary chromium requirements, and it is possible that in situations in which dietary chromium improves insulin function, the supplemental amount is actually replenishing a deficiency in the diet. Heifers supplemented with increasing amounts of chromium had increased insulin sensitivity (166), suggesting that chromium plays an essential role in glucose metabolism in ruminants. Because glucose use predominates during heat stress, chromium supplementation may improve thermal tolerance or production in heat-stressed animals. For instance, supplementing heat-stressed early-lactation dairy cows with chromium reduced the degree of weight loss, improved milk production, reduced plasma NEFA concentrations, and improved rebreeding rates (167,168). In addition, broilers supplemented with dietary chromium and raised in heat-stress conditions had increased feed consumption, body weight gain, and carcass composition traits compared with nonsupplemented birds (169,170). Limited research has been done on other species, but in heat-stressed swine, chromium supplementation did not improve the average daily gain or plasma glucose (171). Further research using varying concentrations and lengths of supplementation should be done to determine the ability of chromium to alleviate the deleterious effects of heat stress.

**Thiazolidinediones.** Thiazolidinediones (TZDs) are a family of drugs that improve insulin sensitivity and are used to treat diabetes. TZDs are synthetic agonists of peroxisome proliferator-activated receptor-γ, an intracellular receptor and transcription factor that upregulates genes involved in cellular glucose uptake (172–175). Because of the improved insulin action, TZDs could be useful for improving and ensuring glucose use and upregulating HSP in heat-stress conditions. Further, TZDs improve heat tolerance in diabetic individuals (176,177) and improves heat-induced HSP72 expression in cardiac muscle of obese diabetic rats (178). In thermoneutral conditions, TZD improves insulin responsiveness of dairy cows (179) and glucose and lipid transporters and insulin receptor gene expression in skeletal muscle of horses (180). If TZDs can enhance HSP production and improve glucose use, it could be a useful strategy during heat stress.

**Conclusions and future directions**

High ambient temperatures have a negative effect on animal and human health and performance. Heat waves can be lethal to humans and animals, and heat stress is responsible
for billions of dollars in losses to global animal agriculture. Consequently, from a human medicine and agricultural perspective, research targeting the identification and implementation of strategies to improve welfare and performance is essential.

Nutrition is a potential avenue to aid human and animal adaptation in hot climates. For instance, heat-stressed animals exposed shift energy metabolism toward carbohydrate use and reduce lipid oxidation. Additionally, it is clear that those with diabetes are at a higher risk of experiencing a heat illness than those without diabetes, and this suggests that adequate insulin action may be essential for adapting to and surviving heat stress. Therefore, diets or nutritional supplements promoting glucose use may be beneficial. There are some indicators that insulin sensitivity is increased by heat stress because HSP expression is increased during heat stress, and these proteins improve insulin function by reducing IRS-1 serine phosphorylation. In fact, therapeutic heat stress increases insulin sensitivity in many species. However, the degree to which insulin action needs augmenting to maintain productivity in heat-stressed conditions remains unknown.

Several nutritional supplements and pharmaceuticals improve insulin action. These include lipoic acid, chromium, and TZDs. Both lipoic acid and chromium improve glucose metabolism in several species during thermoneutral conditions; however, only chromium has been shown to improve production parameters of heat-stressed animals. Similarly, although TZDs improve glucose metabolism in animals exposed to thermoneutral conditions, little is known about its potential to improve production in heat-stressed animals.

Acknowledgment
All authors have read and approved the final manuscript.

Literature Cited


98. Close WH, Mount LE. Energy retention in the pig at several environmental temperatures and levels of feeding. Proc Nutr Soc. 1971;30:33A–4A.


