Chapter 14
Genes Involved in the Thermal Tolerance of Livestock

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Abstract Although there is a good amount of knowledge about the physiological aspects, the effects of heat stress at the cellular and genetic level still remain unrevealed. Functional genomics research is providing new knowledge about the impact of heat stress on livestock production and reproduction. Using functional genomics to identify genes that are up- or down-regulated during a stressful event can lead to the identification of animals that are genetically superior for coping with stress and toward the creation of therapeutic drugs and treatments that target affected genes. Given the complexity of the traits related to adaptation to tropical environments, the discovery of genes controlling these traits is a very difficult task. With the development of molecular biotechnologies, new opportunities are available to characterize gene expression and identify key cellular responses to heat stress. These new tools will enable to improve the accuracy and the efficiency of selection for heat tolerance. Studies evaluating genes identified as participating in the cellular acclimation response from microarray analyses or genome-wide association studies have indicated that heat shock proteins are playing a major role

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in adaptation to thermal stress. Additional genes of interest which two or more studies have identified are the genes for fibroblast growth factor, solute carrier proteins, interluekins, and tick resistance genes. Genes which have only been identified by microarray analysis but not by genome-wide association studies include genes associated with cellular metabolism (phosphofructo kinase, isocitrate dehydrogenase, NADH dehydrogenase, glycosyltransferase, transcription factor, and mitochondrial inositol protein). Other genes of importance were thyroid hormone receptor, insulin-like growth factor II, and annexin.

Keywords Acclimation · Thermal tolerance · Functional genomics · Heat stress

Contents

14.1 Interaction of Animals with Their Environment

Of importance in the livestock industry are the complex physiological adaptive responses of the stress and how they affect the ability of domestic animals to reproduce and produce on an economic basis (Scott 1981). These adaptive responses have been evaluated and measured using two different research approaches; field observations under different seasons, and laboratory experiments using only a given part of the complex climatic factors encountered in the natural environment. Both approaches are necessary for a better understanding of the optimal environmental conditions which yield the highest economic productivity of livestock. Not only are responses of livestock under continued investigations, but emphasis is given to the mechanisms controlling these responses. In addition,

new attention is being directed toward modeling of the complex interactions between the physiological responses and the thermal environment. Many large gaps remain to be bridged, but important accomplishments have been made to ameliorate environmental impacts in improving livestock industry in regions where climatic stress prevails for a significant part of the year (Yousef 1984).

The physical factors that are important to productivity of livestock include air temperature, humidity, solar radiation, and wind speed. Therefore, the microclimate around an animal is thought of as a four-dimensional space (e.g., hot, humid, sunny, windy or hot, dry, sunny, and calm) in which the four independent environmental variables are acting simultaneously and are each time dependent. Mammals may survive, thrive, or die in an unfavorable thermal environment depending on their limit of tolerance and ability to utilize efficient physiological and behavioral mechanisms to maintain a heat balance between their bodies and the environment.

Thermal energy is exchanged between an animal and its environment by radiation, conduction, convection, and evaporation. A conceptual picture of the streams of energy flowing to and from a cow outdoors is shown in Fig. 14.1.

The outermost surface of skin and hair coat of the animal is the transducing surface across which the environment interacts with the internal physiology. As such, the energy flow is a function of the physical properties (hair length, hair-coat thickness and density, color) and optical properties (absorptivity, transmisivity) of the hair coat. Hair-coat and skin characteristics are under genetic and seasonal (acclimatization) control. Animals have developed coping mechanisms to minimize the impact of these environmental stressors on their biological systems. These responses are termed acclimation, acclimatization, and adaptation. Acclimation is defined as the coordinated phenotypic response developed by the animal to a specific stressor in the environment (Fregley 1996) while acclimatization refers to a coordinated response to several simultaneous stressors (e.g. temperature, humidity and photoperiod, Bligh 1976). Generally, there is hardly ever an example under normal environmental conditions where only one variable is changing. Therefore, typically an animal is undergoing acclimatization to a changing environment. Acclimation and acclimatization are induced by the environment and are considered phenotypic and not genotypic change and the responses decay if the stress is removed. Acclimation and acclimatization act to improve the fitness of the animal to the environment. In many cases the response is induced by sudden environmental change such as heat or cold stress. In other examples the acclimation response is driven by seasonal changes in photoperiod or other environmental cues such as the lunar cycle which permit the animal to "anticipate" the coming change in the environment leading to seasonal acclimation adjustments in insulation (coat thickness, fat deposition), feed intake or reproductive activity in advance of the actual environmental change. However, in every case, the process is driven by the endocrine system and is "homeorhetic" meaning metabolism is coordinated to support a specific physiologic state (Bauman and Currie 1980). In this case the specific physiologic state is the "acclimatized animal". If the environmental stressors are present for prolonged

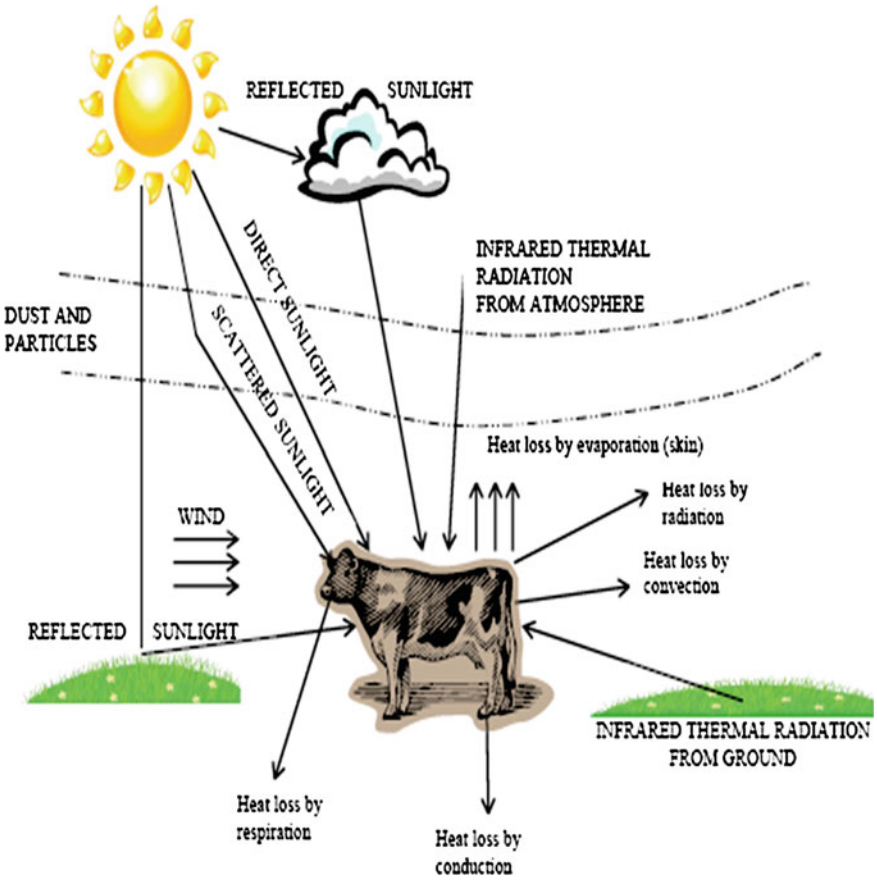

Fig. 14.1 Routes of heat exchange between a cow (outdoors) and its thermal environment include radiation, conduction, convection, and evaporation (from the skin and respiration) as the four basic modes of heat transfer

periods of time (e.g. years) these metabolic and physiologic adjustments can become "fixed genetically" and the animal is considered "adapted" to the environment. For example, *Bos indicus* breeds of cattle have evolved under conditions of high temperature and humidity and display a number of genetic differences which endow them with improved thermotolerance compared to *Bos taurus* breeds of cattle which evolved under temperate weather conditions. *B. indicus* cattle have greater thermoregulatory capability than *B. taurus*. As pointed out by Hansen 2004, *B. indicus* cattle produce less heat, have increased capacity to lose heat toward the environment, or a combination of both. This suggests that low metabolic rates resulting from reduced growth rates and milk yields of many

indicus breeds is a major contributing factor to thermotolerance. The basal metabolic rate of *B. indicus* is infact lower than for *B. taurus*. (Finch 1985). The physiological and cellular basis for this difference have not been identified. One possibility for improved heat loss in *B. indicus* is that the density of arteriovenous anastomoses is higher in *B. indicus*. Since these structures have lower resistance to flow than vascular passages involving capillary networks they facilitate increased blood flow to the skin during heat stress (Hales et al. 1978).

The vascularity and degree of insulation of the skin and quality of the hair coat (hair and skin coat color, thickness and density of hair fibers) also contribute to the effectiveness of heat loss in cattle (Gebremedhin et al. 2008, 2010). All of these are affected by breed and contribute to well-known genotype x environment effects.

14.2 Heat Loss

14.2.1 Sensible Heat Loss

Heat loss from the animal is divided into sensible heat loss and evaporative heat loss. Sensible heat loss comprises heat loss by conduction, convection, and radiation.

Radiant energy exchange occurs between two surfaces as each surface emits energy at wavelengths that are dependent on the temperature of the emitting surface. Infrared radiation refers to radiation of wavelengths longer than those in the visible portion of the spectrum. Convection, however, is heat loss from a surface of an object by fluid (air) flowing over the surface. Convection could be natural (also called free convection) or forced. Free convection occurs when temperature difference in the boundary layer of air surrounding an object causes a movement of the air in response to changes in air density, but forced convection occurs when external pressure difference cause wind to blow past the object. Conduction heat transfer results from the exchange of energy from higher temperature to lower temperature by direct contact of the two surfaces. The heat loss by conduction would be very small when the animal is standing but the surface area in contact to the ground would be about 20% of the total surface area when lying down (Moen 1973). Cows are, however, more likely to stand in sun than lying down because their body temperature increases when lying down because of reduced effective surface area exposure for convective evaporative cooling (Gebremedhin et al. 2011).

Increasing ambient temperature lowers the temperature gradient between the animal and air and consequently decreases the sensible heat loss. Increased air velocity (between 0.5 and 3.0 m/s) over the cow's surface increases convective heat loss by reducing the insulation of the boundary layer, or by reducing the insulation of the hair coat if the velocity is greater than 3.0 m/s (Berman 2004). Higher velocities penetrate into the hair coat and thus increase the convective heat loss from the fur layer and skin surface.

14.2.2 Cutaneous Heat Loss

Various behavioral and autonomic thermoregulatory mechanisms are utilized by cattle to relieve heat stress. A distressed animal may seek shade, change its orientation to the sun, and increase water intake (Blackshaw and Blackshaw 1994). Sweating and panting are two of the primary autonomic responses exhibited by cattle under heat stress. Sweating leads to evaporative heat loss from the skin surface, whereas in panting, sensible heat is used to heat the water vapor and remove heat in the form of vaporized moisture from the lung.

At low ambient temperature, evaporative heat loss represents a small fraction of metabolic heat production. When air temperature is between 10 and 20°C, heat loss by cutaneous evaporation accounts for 20–30% of the total heat loss but when the temperature is greater than 30° C, cutaneous evaporation becomes the primary venue for heat loss, accounting for approximately 85% of the total heat loss, while the rest is lost by respiratory evaporation (Maia et al. 2005). When ambient temperature equals internal body temperature, sensible heat loss is zero and evaporative heat loss via sweating and panting becomes the only available venue for heat loss. Both sweating and panting have the undesirable side effect of depleting body-water reserves.

Cutaneous evaporation is affected by wind velocity, ambient temperature, relative humidity, and thermal and solar radiation. Other factors that affect the efficacy of evaporative cooling from the skin surface are hair-coat physical and optical properties such as hair density, hair length, hair-coat thickness, and hair color. Some of these properties such as hair and skin color may enhance solar absorption and thus increase solar heat load on the skin surface. Other properties such as hair-coat density, which is necessary to provide insulation during cold weather, obstruct free evaporation of water from the skin surface during hot weather resulting in heat stress (Gebremedhin et al. 2008).

Wind greatly increases evaporative heat loss from the skin surface. Wind penetrates the hair coat and reduces the effective thickness of the coat (McArthur 1987). Thermal resistance decreases linearly in hair coat with an increase in air velocity. Increasing air velocity over the hair-coat surface from about 0.2 m/s to about 0.9 m/s raised sweating rate from about 75 g/m^2-h to about 350 g/m^2-h and no further increase in sweating rate occurred as air velocity was increased to 2.2 m/s (Hillman et al. 2001).

Sweating moistens the skin surface and usually leaves the hair-coat layer dry. Wetting the hair coat with a mist of water adds water to the coat surface and penetrates deep down to the skin surface and wets it. The process of evaporative cooling is a complex interaction of humidity and temperature difference between air and skin, air velocity, and hair-coat characteristics such as density and depth. A model incorporating these variables has been developed, where evaporative heat loss resulting from wetting the hair coat as the more effective means of heat loss than sweating (Kimmel et al. 1991). Hillman et al. (2005) reported that heat-stressed cows actively stand under water spray to wet their hair coat. They further

reported that this process lowered core-body temperature. A faster drop in core-body temperature was recorded when the hair coat was sprayed with water at short time intervals between sprays. The decrease in core-body temperature occurred at a faster rate when the spraying is combined with blowing air over the hair coat (Brouk et al. 2003; Hillman et al. 2001).

Gebremedhin et al. (2008) reported that cutaneous moisture production (sweating rate) ranged between 189 ± 84.6 and 522 ± 127.7 g/m^2-h for solar load exposure >500 W/m^2 (average 833 ± 132 W/m^2), average THI of 82.7 ± 1.64, air velocity between 0.8 and 1.2 m/s, and body (rectal) temperature >38.8°C (threshold for heat stress). The same report indicated that in a hot and dry environment, evaporative cooling was profoundly increased (from 68 g/m^2-h before wetting to 508 g/m^2-h after wetting the skin surface, exposed to 0.2 m/s air velocity, and without solar load), and the rate was further increased (from 296 g/m^2-h before wetting to 961 g/m^2-h after wetting) when air velocity over the wetted skin surface was increased to 0.9–1.0 m/s. In a hot and humid environment, however, the increase was relatively modest (from 258 g/m^2-h before wetting to 490 g/m^2-h after wetting) for an air velocity of 0.9–1.0 m/s and a solar load >600 W/m^2. Moisture production is higher in hot and dry conditions than in hot and humid because of higher moisture gradient between the skin surface and ambient air.

A prolonged (extended) exposure to a hot and dry condition or exposure to 3 h of 850 W/m^2 of solar load caused rectal temperature to rise above 40.0°C and respiration rate to rise above 125 breaths/min. Under these conditions, black or predominantly black cows were observed foaming in the mouth, sticking their tongues out, and drooling (Gebremedhin et al. 2010). During these events, immediate intervention with water spray of the body helps to alleviate heat stress. A physiological upper limit of moisture production, which is different for each cow, seems to exist. The maximum sweating rate was about 660 g/m^2-h for dairy cows and feedlot heifers, and the driving force for moisture production seems to be skin temperature (Gebremedhin et al. 2010).

14.2.3 Respiratory Heat Loss

Sweating and panting appear to be under independent control. Energy is lost by vaporizing water within the respiratory tract. The amount of water lost in grams per unit time when multiplied by the latent heat of vaporization of water at the appropriate temperature gives the rate of water loss in energy units.

Maia et al. (2008) developed a model for calculating the heat loss by respiratory evaporation (Q_R, W m^{-2}) and is expressed as:

$$Q_R = \frac{\lambda VF(w_E - w_A)}{60A} \tag{14.1}$$

where, $\lambda = 2500.7879 - 2.3737 * t_A$ is the latent heat of vaporization (Jg^{-1}); A = the body surface area; V (m^3 $breath^{-1}$) = tidal volume; F = respiratory rate (breaths min^{-1}); w_A, w_E (g m^{-3}) are absolute air humidity of the atmosphere and expired air, respectively, and they are given by:

$$w_A = \frac{2166.87 \times P_p\{t_A\}}{273.15 + t_A} \tag{14.2a}$$

$$w_E = \frac{2166.87 \times P_p\{t_E\}}{273.15 + t_E} \tag{14.2b}$$

where, $P_P\{t_A\}$ and $P_P\{t_E\}$ are the partial vapor pressures (kPa) of ambient air and expired air, respectively; t_A and t_E are temperatures (Celsius degree) of ambient and expired air, respectively.

Stowell (2000) suggested that a respiration rate of 80–90 breaths/min was a clear indication of a cow experiencing heat stress.

14.3 Modeling Heat Exchange Between an Animal and the Environment

It is impossible to describe mathematically all of the dynamic thermal relationships between a biological object and its thermal environment, but research on the thermal energy exchange of both plants and animals has provided insight into the mechanisms involved. The climatic energy demands (food and water) for an animal is inherently a coupled heat and mass transfer problem (Fig. 14.2). The energy balance is the diagonal in the figure, and the horizontal expressions represent the food ingested and water consumed (Gebremedhin et al. 1984).

It is obviously impractical to examine experimentally all the possible combinations of radiation, air temperature, wind velocity, animal size, metabolic rate, evaporative water loss, and hair-coat physical and optical properties. There are considerable experimental difficulties in measuring accurately animal thermal responses in their natural habitat. Therefore, mechanistic models have to be developed to simulate the energy exchange between the animal and its environment and be able to evaluate what if conditions.

The analysis given below is for a steady-state situation. However, much of the time, an animal is in a transient energy state as it moves about in the environment. While in transient states, the energy budget for an animal must average within the environmental limits permitted by the steady-state requirements for survival. An animal may search for food in an environment which is intolerable to it as a steady-state situation, provided it is in this environment for a short period of time compared to the body-time constant of the animal.

A basic concept of a one-dimensional mechanistic heat transfer model through artificial fur layer was described by Kowalski and Mitchell (1979) and through

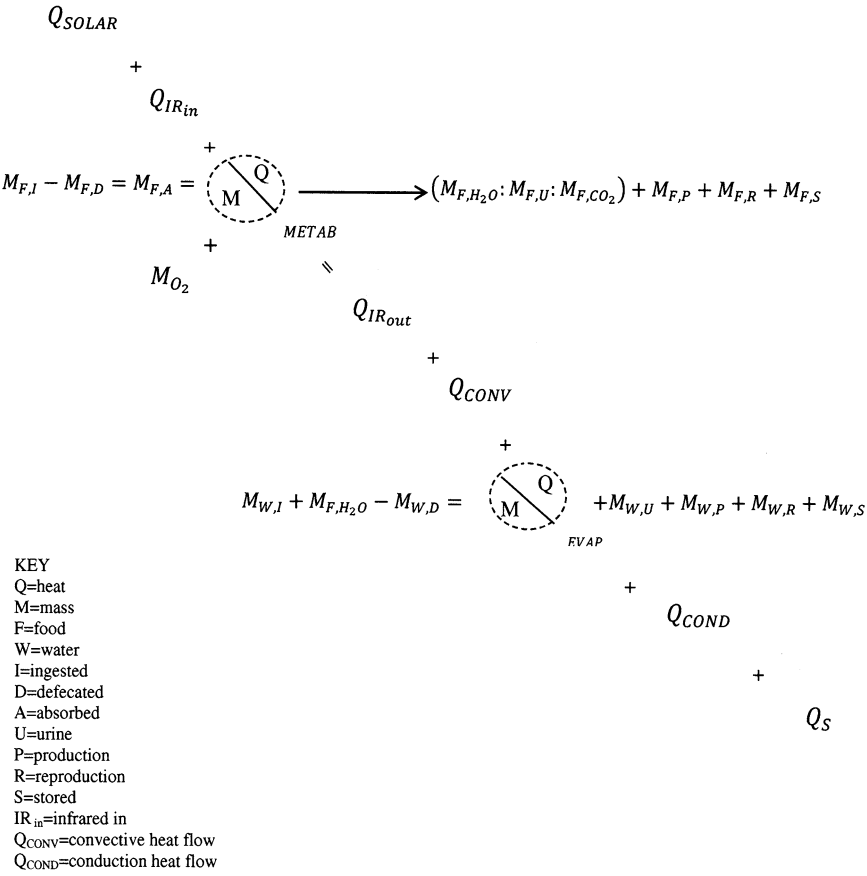

Fig. 14.2 Climatic energy demand (feed and water) for livestock (Gebremedhin et al. 1984)

animal hair coat by Gebremedhin et al. (1983). The model is a function of environmental parameters and hair-coat physical properties. The absorbed solar radiation, q''_{solar},within the hair coat was incorporated into the model as an internal heat generation source. The model describes the energy transport through the hair coat and the solution provides the temperature profile through the hair coat. The model is developed from basic principles where conduction heat flux, q''_c, and radiation, q''_r heat flux enters into and leaves out of the element at both the top and bottom of a section of hair coat (Fig. 14.3). The effective conductivity, k_{eff}, accounts for the physical properties of the hair coat.

An energy balance on the incremental element yields the differential equation which describes the temperature profile through the hair coat. After solving for the temperature profile, the heat loss through the hair coat can be determined from an energy balance on the skin surface (Gebremedhin et al. 1983). Heat loss is directly

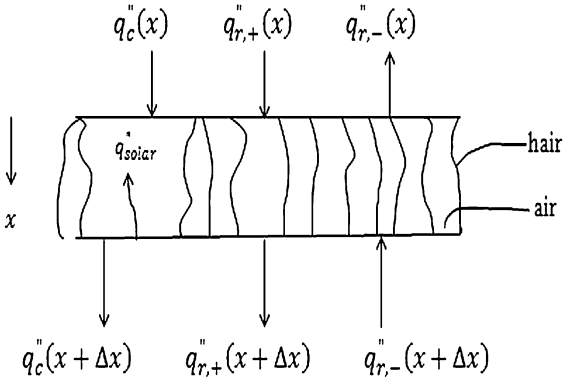

Fig. 14.3 Heat flow within an incremental element of hair coat

related to metabolism and, therefore, to feed requirements for survival, production (or growth), and reproduction potential. The energy balance is expressed as

$$\underbrace{k_{\text{eff}}\frac{\mathrm{d}^2T}{\mathrm{d}x^2}}_{\text{Conduction term}} - \underbrace{\underbrace{\frac{\mathrm{d}q''_{r,+}(x)}{\mathrm{d}x}}_{\text{Inward flux}} + \underbrace{\frac{\mathrm{d}q''_{r,-}(x)}{\mathrm{d}x}}_{\text{Outward flux}}}_{\text{Long-wave irradiation}} + \underbrace{q''_{\text{solar}}}_{\text{Solar}} = 0 \tag{14.3}$$

Two boundary conditions are needed to solve Eq. 14.3 and are expressed below:

$$\text{at } z = z_L \quad -k_{\text{eff}}\left.\frac{\mathrm{d}T}{\mathrm{d}z}\right|_{z_L} = h_c(T(z_L) - T_{\text{air}}) \tag{14.4a}$$

$$\text{at } z = 0 \quad T(0) = T_{\text{Skin}} \tag{14.4b}$$

In the first boundary condition, the energy conducted to the hair-coat-air interface equals the energy convected from that surface. This boundary condition couples the outer hair-coat surface to the prevailing wind conditions through the convective heat transfer coefficient, h_c, and ambient air temperature, T_{air}. The second boundary condition is the temperature at the skin surface, $z = 0$. It may be either specified or measured. More details of this model is given in Gebremedhin et al. (1983).

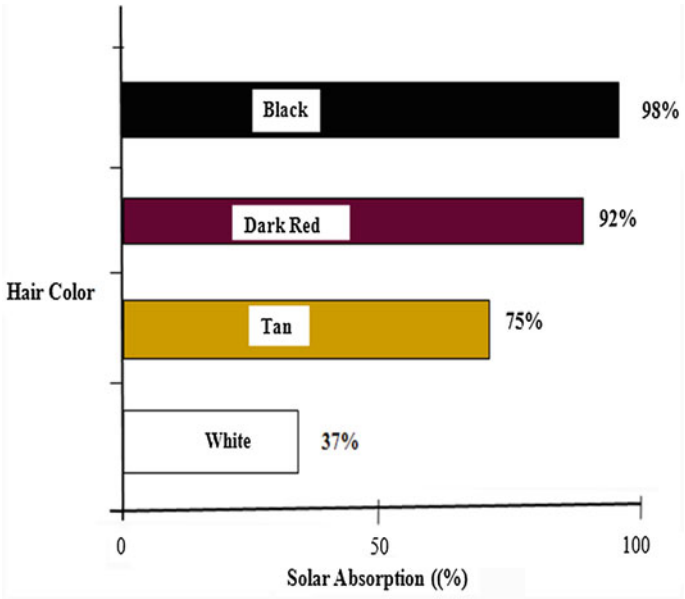

Fig. 14.4 Relationship between hair color and solar absorption for four breeds of heifers (*black* Angus, *dark-red* MARC III, *tan-colored* MARC I, and *white* Charolais) (Gebremedhin et al. 2011)

14.4 Effects of Hair Coat Physical and Optical Properties on Heat Exchange

Hair and feathers do not merely provide insulation from the cold, but from heat as well. They tend to ameliorate the thermal regime of the body proper by buffering the thermal variations.

The effect of direct solar radiation on the radiant temperature over the entire surface of an animal is not uniform because both the color of this surface and the angle of the rays striking the surface are important in determining just how much solar energy is absorbed. The relationship between hair color and solar absorption for four breeds of heifers is shown in Fig. 14.4.

In a study on the effect of hair color on thermoregulation, Hillman et al. (2001) reported that when black Holstein cows were exposed to direct sunlight, their surface temperature increased by 4.8°C, and by 0.7°C for white cows. The difference in temperature between black and white is because of higher solar absorption by black than white. They also reported that rectal temperature increased at a rate of 0.7°C/h for black cows and 0.3°C/h for white cows. In another study (Hillman et al. 2005), they reported an increase in sensible heat flux in the order of 26% for dark-red, 22% for black, 5% for tan, and 4% for white.

Da Silva et al. (2003) investigated radiative properties of the skin and hair coat of various breeds of cattle with respect to shortwave radiation. The study

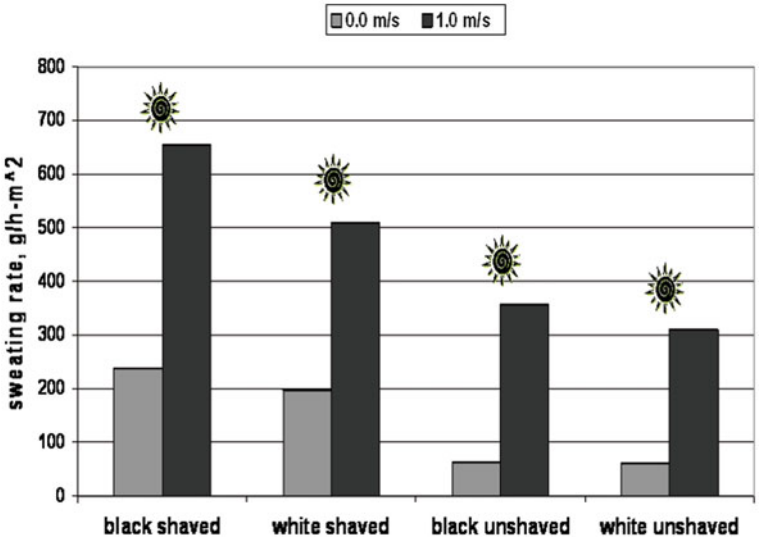

Fig. 14.5 Average sweating rates of cows with black and white hair coats shaved or unshaved under direct sunlight at zero air velocity, and 1.0 m/s (Gebremedhin et al. 2007)

concluded that light-hair coats exhibited much higher reflectivity than dark-hair coats for wavelengths ranging from 300 to 850 nm.

The presence of a hair coat conserves heat by entrapping air. The entrapped air serves as insulation in the case of cold environments but becomes an obstruction to evaporation of moisture from the skin surface in the case of hot environments. This was substantiated by measuring sweating rates from shaved and unshaved areas of a cow (Gebremedhin et al. 2007). Sweating rates from the shaved areas were higher than those from the unshaved areas, regardless of hair-coat color (Fig. 14.5). On the average, sweating rate from black shaved areas was 1.84 times higher (655 g/h-m^2) than that from unshaved black hair coat (356 g/h-m^2). Similarly, sweating rate from a white shaved area was 1.64 times higher (509 g/h-m^2) than that from unshaved white hair coat (310 g/h-m^2). On the shaved areas, the conversion of sensible heat to latent heat is unobstructed because sweat (water) on the skin surface is exposed directly to ambient air and solar radiation. On the unshaved areas, however, the presence of hair coat above the sweat glands might be acting as a moisture trap creating locally a more humid environment. Thus, the presence of moisture in the hair coat results in lowering the moisture gradient between the skin surface and the hair layer above it, causing less evaporation to take place, and consequently depressing heat loss from the skin surface. The presence of a hair coat, therefore, becomes a liability i.e., obstructing evaporative cooling of the skin surface in hot environments. That is perhaps why cows shed some of their hair during summer.

14.5 Genetics of Hair Coat

Several loci and some genes have been identified as having involvement in coat color and quality as well as heat dissipation, Olson et al. (2006). These changes are all adaptive in nature and are genetically fixed in their populations.

14.6 Acclimation and Adaptation to Thermal Stress

When animals are adapted, the physiologic differences between them and non-adapted animals do not disappear when the environment changes. This is not the case in acclimation where differences do disappear if the stress is removed. However, it is becoming apparent that the systems which are involved in acclimatization are the same systems which endow animals with thermotolerance or adaptation to heat. Therefore, obtaining a better definition of the gene networks up- and down-regulated in response to environmental stress will also lead us to those pathways which offer promise to improve thermotolerance.

Acclimatization is a homeorhetic process which requires several days to weeks to fully develop. There is a hormonal link between the central nervous system and the effector cell types involved and the end result of the hormonal change is to alter the responsiveness of the effector cells to environmental change (Blighs 1976). These key features are hallmarks of a homeorhetic process where metabolism of multiple tissues and organs are coordinated to support the new acclimatized state as contrasted to a homeostatic process, (Bauman and Currie 1980, Collier et al. 2005), where regulation is occurring around a set point. We then should consider the stages of acclimation, the hormones that are driving acclimation and what changes are occurring in effector tissues to accomplish development of the acclimatized state.

14.7 Stages of Acclimatization

Acclimatization is generally considered to occur in two stages; acute or short term and chronic or long term (Johnson and Vanjonack 1976; Horowitz 2002; Garrett et al. 2009). The acute phase includes the shock response at the cellular level, (Carper et al. 1987; Sonna 2002) and homeostatic endocrine, physiological, and metabolic responses at the systemic level while the chronic or long-term phase results in acclimation to the stressor and involves reprograming of gene expression and metabolism, (Horowitz 2002; Collier et al. 2006b).

In agricultural animals there is typically a loss in productivity as animals progress through the acute phase and some or even all of this productivity is restored as animals undergo acclimation to the stress.

14.7.1 Systemic Response

The systemic response to environmental stress is driven by two systems—(1) the central nervous system (CNS) and (2) peripheral nervous system and endocrine components (Charmandari et al. 2005). The central component is comprised of nuclei in the hypothalamus and the brainstem which releases corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). The peripheral components of the stress system include the pituitary-adrenal axis, the efferent sympathetic-adrenomedullary system, and components of the parasympathetic system (Habib et al. 2001). However, relative to environmental stress and acclimation the initial phases of the response involve receptor systems at the periphery which drive autonomic and endocrine responses to the changing environment such as skin thermoreceptors and photoreceptors in the retina.

Sweating and panting are two of the primary autonomic responses exhibited by animals under heat stress. Sweating results in increased evaporative heat loss from the skin surface, whereas in panting, sensible heat from the body core is used to heat the water vapor and expel heat in the form of vaporized moisture from the lungs. However, these responses are likely driven more by surface than core-body temperatures, evaporative heat loss from skin and the respiratory tract is highly correlated with skin temperature. In fact, skin temperature is more highly correlated with these parameters than core temperature suggesting that thermal receptors in the skin initiate the autonomic systemic response to thermal stress. Another potential route of information flow from the surface to the whole system would be via secreted heat shock protein released from skin epithelium during heat stress which would act as an alarm system to assist in mobilizing the acute response to thermal shock. An examination of the relationship between skin temperature and expression of the gene for inducible heat shock protein 70 revealed that gene expression is increased several fold as skin temperature approaches 35°C which is below body temperature but represents the upper limit of the thermoneutral zone of cattle. Berman (2005) estimated that the stress response system in cattle would be activated at effective temperatures at and above 35°C. Previously, it has been demonstrated that evaporative heat loss and rectal temperature rise dramatically above an effective environmental temperature of 35°C, Collier et al. 2008a). It is now apparent that the heat shock response in bovine skin epithelial tissue is activated at effective environmental temperature of 35°C as well. Activation of the heat shock response in cells in many cases leads to secretions of HSP's into the extracellular space and plasma, Ireland et al. 2007)

Recently, secreted HSP was identified in plasma of cattle. Kristensen et al. (2004) and Gaughan and Bonner (2009) have demonstrated that secreted HSP concentrations rise in plasma when the effective environmental temperature exceeds 35°C.

Thus, activation of the heat shock response in cells also leads to secretion of Hsps into the extracellular space and plasma, (Ireland et al. 2007). It has been hypothesized that secreted heat shock protein acts as an alarm signal for the

immune system and several measures of innate immunity are increased following increases in secreted heat shock protein in blood (Fleshner and Johnson 2005). Secreted heat shock protein has also been shown to improve survival of neural cells subjected to environmental and metabolic stressors, (Tytell 2005; Guzhova et al. 2001).

Thus, the acute response in cattle is initially driven by thermal receptors in skin which activate the central nervous system and subsequently, the endocrine system and the peripheral components of the autonomic system. This response is augmented by secreted heat shock proteins which rapidly rise in plasma and are believed to provide protective effects to a variety of cell types as well as activating the innate immune system. At a skin surface temperature of 35°C the respiration rate of cattle will reach or exceed half maximal which is about 60–70 breaths/min. At this point, the animal is entering the acute phase of the stress response.

During the acute phase there is rapid decline in productivity of domestic animals and this is especially true in high producing dairy cows. The decline in productivity begins on the day the stress is initiated but is not maximal until 48 h following the initiation of the stress (Collier et al. 1981). This suggests that there are intermediate events between the rise in body temperature and the reduction in milk yield. Rhoads et al. (2009) demonstrated that reduced feed intake only accounted for 40% of the decline in milk yield and that other factors were likely involved in the rapid decline in production due to severe heat stress. They postulated that reduced glucose availability could potentially reduce lactose synthesis rates and contribute to the reduced milk volume. Silanikove et al. (2009) reported that acute heat stress reduced milk secretion in lactating cows by up-regulating the activity of a milk-borne negative feedback regulatory system, specifically an n-terminal fragment of β-casein. They also reported that this fragment has an inhibitory activity on the mammary epithelial cell potassium channel. Identification of the exact mechanisms by which milk yield is reduced in response to heat stress offers potential in improving productivity of animals in warm climates.

After 5–7 days of continuous stress, animals enter the chronic "acclimation" phase of the stress response. During this phase there is a reprograming of metabolism resulting in altered responses to homeostatic signals. The overall impact of these changes is a reduction in the impact of the stress on the animal. The transition of animals from the acute to the chronic phase of the stress response has been extensively studied in laboratory models by Horowitz and coworkers (Horowitz 2002; Horowitz et al. 2004; Maloyan et al. 2005; Horowitz 2007). These changes are driven by the endocrine system and result in global changes in gene expression as well as post-translational alterations in protein function. Hormones which have been identified as being homeorhetic regulators are also linked to acclimation responses to thermal stress and changes in photoperiod related to season. These include somatotropin, prolactin, thyroid hormones, glucocorticoids, and mineralocorticoids. Several of these hormones are known to contribute to regulation of HSP gene expression.

The changes which occur at the cellular level which provide improved cytoprotection are described in the section on the cellular response to heat stress.

Table 14.1 Genes associated with heat shock response and/or acclimation to warm climates

Gene	References
Heat shock proteins	1, 2, 3
Interleukins	1, 3
Keratins	1, 3
Fibroblast growth factor	1, 2
CD antigen	3
Solute carrier family	1, 3
NADH dehydrogenase	1
Tick resistance genes	1, 3
Collagen, type VI	1
Kinesin family	1
Selenium binding protein	1
Annexin	1
Glycosyltransferase	1
Protein kinase C	1
Transcription factor	1
Bcl2 associated anthanogene 3	1
Zinc finger	1
Thyroid hormone receptor	1
Mitochondrial inositol Protein	1
Isocitrate dehydrogenase	1
Butyrophilin 3	1
Phosphofructo kinase	1
Insulin-like growth factor II	1

References: 1. Collier et al. 2006b; 2. Hayes et al. 2009; 3. Chan et al. 2010

At the systemic level, metabolism is coordinated to support a new physiological state. Some of the changes which occur include a lowering of the threshold for vasodilation and evaporative cooling (Roberts et al. 1977), reduced metabolic rate, increased resistance to thermal injury, and improved cardiac performance, (Horowitz 2002). Endocrine changes occurring with acclimation to heat stress in cattle include increased plasma prolactin, reduced glucocorticoid, somatotropin, and thyroxin concentrations, increased progesterone concentrations and decreased estrone sulfate concentrations in pregnant cattle (Collier et al. 2005). Somatotropin is a homeorhetic regulator and has been shown to be beneficial in improving evaporative heat loss and thermal balance in cattle during summer heat stress (Manulu et al. 1991).

Despite large reductions in feed intake and energy balance during heat stress there appears to be a tighter coupling of the somatotropin-IGF axis during summer resulting in higher IGF concentrations during summer months compared to winter months and only slight decreases in plasma IGF to severe heat stress even when somatotropin concentrations are reduced, (Collier et al. 2008b; Rhoads et al. 2009). This fact reinforces the importance of somatotropin in dealing with environmental stress, (Collier et al. 2005). Additionally, the somatotropin response to GRF is not affected by severe heat stress, (Rhoads et al. 2009). The seasonal variation in

coupling of the growth hormone-IGF axis is also associated with effects of increased photoperiod on growth rate and milk yield in cattle, (Collier et al. 2006a).

14.7.2 Cellular Responses

Heat tolerance at the cellular level is directly related to the ability of the cell to maintain elevated levels of heat shock proteins (HSP's). As stated by Horowitz and Assadi (2010) "A hallmark of the acclimation process is the enhancement of cytoprotective networks-that of the heat shock proteins, anti-oxidative and apoptotic-and the stabilization of the Hypoxia Inducible Factor- Iα, the master regulator of oxygen homeostasis".

The heat shock response of bovine embryos and mammary epithelial cells to heat stress has been described (Edwards et al. 1997; Jousan and Hansen 2004; Collier et al. 2006b, 2008a). The dramatic effect of heat shock on mammary epithelial cell growth and structure has been well described (Collier et al. 2008a). Heat shock acutely downregulates DNA synthesis and adversely affects the ability of cells to maintain their cytoskeleton leading to a collapse of cell structure.

The transcriptome profile of heat-shocked bovine mammary epithelial cells indicated down-regulation of genes involved in cell structure, DNA synthesis, cell division, metabolism, biosynthesis, and intracellular transport while genes associated with cellular and protein repair and degradation were up-regulated. The heat shock response is induced by accumulation of mis-folded proteins in the cytoplasm and is mediated by heat shock transcription factors (HSF), (Voellmy and Boellmann 2007; Horowitz and Robinson 2007). There are four forms of HSF but HSF-1 is considered to be the primary transcription factor involved in the heat shock response, (Akerfelt et al. 2007). Regulation of HSF-1 activity has been reported to be largely controlled post-translationally and not at the level of synthesis/degradation of the transcription factor, (Voellmy and Boellmann 2007). Once activated the HSF-1 monomer trimerizes with other HSF-1 molecules which is essential for DNA binding (Sarge et al. 1993). The activated complex can then enter the nucleus and initiate transcription of heat shock proteins.

Genes currently identified as participating in the cellular acclimation response are shown in Table 14.1. These genes were either identified from microarray analysis (Collier et al. 2006b) or genome-wide association studies (Hayes et al. 2009; Chan et al. 2010). All three studies indicate that HSPs are playing a key role in acclimation and adaptation to thermal stress. Additonal genes of interest which two or more studies have identified are the genes for fibroblast growth factor, solute carrier proteins, interluekins, and tick resistance genes. Genes which have only been identified by microarray analysis but not by genome-wide association studies include genes associated with cellular metabolism (phosphofructo Kinase, isocitrate dehydrogenase, NADH dehydrogenase, glycosyltransferase, transcription factor, and mitochondrial inositol protein). Other genes

of importance were thyroid hormone receptor, insulin-like growth factor II, and annexin.

Thermal acclimation and thermal adaptation is associated with increased basal levels of HSPs (Carper et al. 1987; Kregel 2002; Maloyan et al. 1999). Thermal acclimation and cyclopentenone prostaglandins have been shown to increase the DNA-binding activity of HSF-1 leading to increased HSP gene transcription (Amici et al. 1992; Strauss and Glass 2001; Ianaro et al. 2003; Buckley and Hofmann 2002). Several investigators have shown that heat acclimation also provides cross-tolerance against other types of stress such as hypoxia, ischemia, acidosis, and energy depletion, (Horowitz 2002; Kregel et al. 2002) and that HSF-1 is involved in this process.

Although there is little evidence for endocrine regulation of HSF-1 gene expression activity, there is substantial evidence that expression of heat shock proteins and other cytoprotective proteins are modulated by the endocrine system (Xu et al. 1996)

The separate evolution of *B. taurus*, *B. indicus*, and *Sanga* cattle has resulted in differing genotypes of *B. indicus* and *Sanga* cattle that confer improved thermotolerance compared to *B. taurus* cattle in both beef and dairy populations (Paula-Lopes et al. 2003; Hansen 2004). In addition, large genotype x environment interactions in dairy cattle for milk yield (Cerón-Muñoz et al. 2004; Ravagnolo et al. 2000; Bohmanova et al. 2006) of Holstein cattle indicates that there is considerable opportunity to improve thermal resistance and performance in dairy cattle. These differences include thermoregulatory capability, feed intake, and production responses and cellular differences in heat shock responses, (Hansen 2004; Collier et al. 2008a).

There are genetic differences in cellular resistance to elevated temperature in cattle. It is possible that the same gene or genes conferring cellular thermotolerance are present in Indicus, Senepol, and Romosinuano, especially because of the contribution of *B. indicus* genotypes to these two other breeds (Magee et al. 2002). An alternative explanation is that distinct thermotolerance genes are present in the different genotypes. Identification of the genes conferring cellular thermotolerance offers the possibility of transferring these genes to heat-sensitive breeds to improve reproduction and other physiological systems compromised by hyperthermia. Little is known regarding the molecular basis for the improved cellular resistance to elevated temperature in thermotolerant cattle. There were no detectable differences between Indicus, Senepol, and Angus in the amount of heat shock protein 70 (HSP70) in heat-shocked lymphocytes (Kamwanja et al. 1994) although the tendency for lower cellular concentration of HSP's in Brahman and Senepol may indicate that protein denaturation in response to elevated temperature (one of the signals for HSP70 synthesis; Shamovsky and Nudler 2008) is reduced in Brahman and Senepol. The capacity for transcription in response to elevated temperature seems to be important for expression of genetic differences because there were no differences between Indicus and Holstein embryos in resistance to elevated temperature at the two-cell stage, a time when the embryonic genome is largely inactive, (Hansen 2004). Also, in vitro effects of elevated temperature on

spermatozoa were similar for Indicus, Indicus-influenced breeds, Angus, and Holstein (Block et al. 2002).

The cellular thermotolerance of crossbred embryos is dependent upon the genotype of the oocyte and not the spermatozoa. Embryos produced by insemination of Brahman oocytes with Angus spermatozoa were more thermotolerant than embryos produced by insemination of Holstein oocytes with Angus semen (Block et al. 2002). In contrast, there were no differences in thermotolerance between Indicus × Holstein embryos and Angus × Holstein embryos. These results indicate that either genes conferring thermotolerance are paternally imprinted (only the maternal allele being expressed) or that thermotolerance in embryos depends upon some genetically controlled factor produced in the oocyte. Regulation of body temperature is the most critical factor for genetic differences in reproductive function during heat stress since the depression in fertility per unit increase in body temperature is the same for *B. indicus* × *B. taurus* crossbred cows as for Hereford × Shorthorn cows (Hansen 2004).

New genomics tools are also beginning to provide information on specific gene networks associated with thermotolerance. Lillehammer et al. (2009) identified single nucleotide polymorphisms (SNPs) that were associated with gene by environment interactions for production traits in cattle. Hayes et al. (2009) also reported on a genome-wide association study aimed at identifying differences related to adaptation to environmental change. It is envisioned that, in the not too distant future, use of SNP markers will lead to greater progress in improving thermotolerance of high producing dairy breeds.

Acclimation is a homeorhetic process driven by the endocrine system which enables animals to respond to a stress. The resulting cellular, metabolic, and systemic changes associated with acclimation reduce the impact of the stress on the animal and allow it to function more effectively in the stressful environment. These changes are lost if the stress is removed, so the process is not based on changes in the genome. However, if the stressful environment is not removed over successive generations these changes will become "genetically fixed" and are referred to as adaptations. A better understanding of genetic differences between adapted animals will contribute useful information on the genes associated with acclimation. Likewise, study of gene expression changes during acclimation will assist in identifying genes associated with improved thermotolerance.

14.8 Reproduction

The primary objective of the reproductive process is to produce a viable and healthy offspring. Heat stress has been shown to negatively impact livestock reproduction. Over 50% of the world's livestock reside in tropical regions where temperature or more specifically, the temperature humidity index often exceeds thresholds reaching levels that have been shown to impair reproduction as well as

other aspects of livestock performance. As compared to European breeds, zebu cattle experience less severe reduction in reproductive function (Hansen 2004).

However, differences exist between a multitude of genomic and environmental factors as well as their interactions determine animal performance by affecting several major components involved in male and female reproductive function. Heat stress, in general, has deleterious effects on the reproductive process across mammalian species. However, certain breeds have adapted genetically to cope with heat stress and experience less severe reductions in reproductive function due to elevations in temperature. Recent improvements in management and feeding strategies in livestock have stemmed from improved understanding and ability to regulate physical environment surrounding the animal and elucidation of physiological mechanisms that govern animal nutrition, metabolism, reproduction, and lactation. Emerging research in the field of genomics is uncovering additional, promising avenues by which to improve animal production, breeding

There is a general belief that the appendages of *B. indicus* cattle contribute to the superior thermoregulatory ability of these cattle since they increase the surface area per unit body weight as compared to *B. taurus*. The actual importance of these anatomical features is not likely to be crucial for thermoregulation; because surgical removal of the dewlap or hump of Red Sindhi bulls did not have a measurable impact on thermoregulatory ability (McDowell 1958). Additionally, differences in regulation of rectal temperature in response to heat stress were observed between Jersey and Red Sindhi × Jersey even though surface area per unit body weight or metabolic body weight was similar between the two genotypes.

14.8.1 Placenta

14.8.1.1 Ruminant Placenta

Heat stress has long been known to impair reproductive function in cattle, sheep, and swine species. These losses are largely attributed to failure of embryonic implantation and early embryonic loss as a result of heat stress during early pregnancy. However, it has become apparent that that heat stress during mid- and late-gestation also contributes significantly to reductions in fetal survival and birth weight which are associated with decreased placental weight. Although the exact mechanism by which heat stress reduces fetal survival and birth weight are not yet known, several studies have identified maternal, fetal, and placental molecular deficiencies and differences in gene expression that may serve as lead to the development of screening methods for genetic markers to improve breeding and other management practices by identifying and exploiting genes associated with thermal tolerance traits.

The placenta is a temporary organ, present only in eutherian animals during pregnancy, is comprised of cells from both maternal and fetal origin and facilitates

fetal-maternal exchange of nutrients, gasses, hormones, and waste products. The placenta begins to form early during pregnancy and attaches to the uterus in a process referred to as implantation. The second trimester is characterized by rapid placental growth and development, which precedes and facilitates the subsequent rapid fetal growth phase that defines the third trimester. In mammals, 95% of birth weight is accumulated by the fetus during the second half of gestation.

Our current understanding of the ruminant placenta and its function has been gained from observations on the effects of environmental heat stress on livestock animal reproduction in production settings as well as in controlled experimental investigations utilizing various animal models of placental insufficiency and fetal growth restriction. The ruminant placenta is classified as cotyledonary and typically contains 60–100 placentomes in sheep and 70–120 placentomes in cattle. The placentome is composed of a maternal component, the caruncle, and a fetal component, the cotyledon, which together comprise a fetal-maternal exhchange unit, the placentome, which is characterized by an intricate capillary network that serves to facilitate fetal-maternal exchange of nutrients, electrolytes, gasses, hormones, and waste products, while serving as a barrier to prevent the passage of larger items such as blood cells, immune system components, and large molecules (Mossman 1987).

Fetal growth is directly related to placental mass (Reynolds et al. 2005; Myers et al. 1982) and importantly also to the proper development of the placental microvasculature (Kingdom and Kaufmann 1997; Grazul-Bilska et al. 2010, 2011). Heat stress exerts deleterious effects on placental mass, microanatomical development, and function of the placentome (Kingdom and Kaufmann 1997; Regnault et al. 2002). The degree to which heat stress impairs placental mass and function depends on the timing, duration, and severity of the heat stress (Hafez 1964). In the ewe, heat stress prior to breeding and during the first trimester is associated with increased embryonic loss and disruptions in the process of implantation (Dutt 1963) reflected by a reduction in the number of placentomes formed.

Heat stress initiated at the onset and limited in duration to the second trimester (approximately 40–95 days gestation in the sheep, term = 148 days), a period beginning after implantation has completed and ending prior to the onset of the rapid fetal growth, is sufficient to elicit a greater than 50% reduction in placental mass (Bell et al. 1989) and is associated with decreased placental mass, altered placentome morphology, and decreased placental transport function (Alexander and Williams 1971). Microscopic imaging of placentomes of heat-stressed pregnant ewes reveals increased tortuosity and sinusoidal structuring of the microvasculature (Hafez et al. 2010), which is thought to be a compensatory mechanism to increase surface area and decrease resistance to blood flow thereby increasing exchange efficiency of the smaller placenta.

Although reductions to placental mass due to heat stress occur during the second trimester, the effects on fetal growth restriction become apparent and progressively worsen over the course of the third trimester. It is thought that even a compromised placenta is capable of transporting an adequate supply of oxygen and

nutrients to meet fetal demands for the first two trimesters, but becomes insufficient when challenged by rapid increases in fetal nutrient and oxygen demands that coincide with the fetal growth during the third trimester. Some studies suggest that fetal growth restriction is secondary to the effect of heat stress on placental mass while other studies in which heat stress was initiated during the second trimester and prolonged into the third trimester revealed additional fetal and placental growth restriction (Galan et al. 1999) demonstrating that the timing and duration of heat stress during gestation is a direct determinant of fetal growth restriction.

In addition to the impact on placental mass and morphology, heat stress alters the maternal endocrine profile and in cows this is associated with reduced calf birth weight and subsequent milk yield (Collier et al. 1982). Catecholamines are markedly elevated in the heat stress-induced PI-IUGR fetus and alter cotyledonary blood flow and fetal glucose metabolism (Yates et al. 2011). In addition to hemodynamic changes, heat stress induces alterations to the regulation of gene expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) (Regnault et al. 2002) which play major roles in vascular development within the placentome (Ahmed et al. 2000).

During normal placental development, capacity for nutrient and gas exchange increases with gestation as fetal demands increase over the third trimester. This increase in placental capacity is achieved by increasing uterine blood flow (Christenson and Prior 1978), but also, importantly, by branching and expansion of the microvasculature within the placentome to increase capillary surface area for exchange (Leiser et al. 1997). Heat stress, in addition to decreasing uterine blood flow (Regnault et al. 2007), disrupts all major routes for placental nutrient and gas exchange, namely, diffusion, facilitated diffusion, and active transport. Diffusion capacity for oxygen across the placenta is markedly reduced in the ovine model of heat stress-induced placental insufficiency induced intrauterine growth restriction (PI-IUGR) (Regnault et al. 2007), which is reflected by fetal hypoxemia (Thureen et al. 1992) and this is associated with decreased expression of VEGFR-1 mRNA in the fetal cotyledon and increased expression of Growth Factor (PlGF) in the maternal caruncle (Regnault et al. 2003). Interestingly, when oxygen transport is normalized to fetal weight, no difference in oxygen transport between PI-IUGR and normal animals exists (Ansari et al. 2003) suggesting that oxygen availability is sensed by the fetus or placenta and may be an important determinant of fetal growth.

The mammalian fetus relies heavily on glucose as an energy source for growth and development (Battaglia and Meschia 1978). Fetal glucose supply is derived almost exclusively from maternal circulation via facilitated diffusion across the placenta via glucose transporter proteins (Olson and Pessin 1996). Fetal plasma glucose concentrations are reduced in PI-IUGR sheep fetuses compared to control fetuses, and the deficiency becomes increasingly pronounced as the third trimester progresses and fetal mass and demand for glucose increases (Bell and Ehrhardt 2002). The expression of glucose transporter protein isoforms GLUT-1 (Limesand unpublished data) and GLUT-8 (Limesand et al. 2004) is decreased in the placenta of heat-stressed ewes, representing specific mechanisms by which thermal stress

alters placental function and fetal nutrition. Additionally, active transport processes have been shown to be impaired by heat stress as placental amino acid transport (De Vrijer et al. 2004), (Ross et al. 1996), and utilization rates (Regnault et al. 2005) are reduced in heat stress-induced PI-IUGR. In a rat model of nutrient restriction induced PI-IUGR, placental active transport of amino acids are associated with down-regulation of mRNA expression of a number of placental essential amino acid transporters (Jansson and Powell 1998; Norberg and Jansson 1998).

In summary, heat stress during gestation exerts deleterious effects on the ruminant placenta. Placental mass, transport function, and the consequential effects on fetal growth have been well documented. Recent studies have identified specific molecular mechanisms and altered gene expression induced by heat stress, representing potential targets to improve breeding and management practices.

14.9 Fetus

Offspring that are born small for gestational age tend to exhibit substandard performance in terms of growth and carcass qualities and are more likely develop metabolic complications postnatally (Barker et al. 1993), resulting in less accretion of lean soft tissue and more adipose tissue. Additionally, the effects of fetal growth restriction have been shown to be intergenerational as growth-restricted female offspring tends to produce smaller offspring of their own and both have an increased risk of cardiovascular and metabolic complications in adolescence and adulthood (Drake and Walker 2004).

Heat stress has negative impact on several aspects of livestock animal reproduction. However, within a species, breed differences in thermal tolerance and associated degrees of impairment to various aspects of male and female reproductive function highlight the importance of genetics. Animals that are adapted to warm climates generally exhibit less impairment of reproductive functions due to heat stress which is in part due to enhanced ability to regulate body temperature and dissipate heat during periods of increased temperature and humidity. Interestingly, cells isolated from these animals and studied in vitro continue to exhibit enhanced survival and function compared to cells from breeds not adapted to thermal stress despite isolation from total body thermoregulatory effects. This phenomenon indicates that at least one component of thermal tolerance is regulated at the cellular level independently of total body thermal regulatory functions. Current studies aim to elucidate the genetic basis and molecular mechanisms by which cells from certain breeds are exceptionally resistant to thermal stress while cells from less-adapted breeds experience high losses in cell function and survival. Additionally, heat stress during gestation has been shown to alter fetal gene expression, metabolism and subsequently growth. The effects of heat stress on fetal growth restriction have been shown to persist into adulthood, which, from a

livestock production standpoint, translates to decreased animal performance and carcass qualities.

14.9.1 Fetal Gene Expression

The effects of heat stress on livestock reproduction in terms of conception, embryonic survival, and birth weight have long been known. Recent advances in the physiological understanding of processes that regulate animal reproduction highlight the importance of genetics as a target for strategies to enhance breeding programs and production management practices. Additionally, research utilizing facilities where environmental conditions such as temperature, humidity, and ultraviolet radiation can be experimentally manipulated have led to major advances in our understanding the effects of heat stress on various aspects of livestock reproduction and fetal development.

The increased metabolic expenditure associated with pregnancy generates copious amounts of heat in the ruminant. As a result, fetal temperature in a normal pregnancy is approximately 0.3–1.0°C higher than maternal body temperature (Power 1989). Under thermal neutral conditions, maternal thermoregulatory mechanisms adequately dissipate heat such that the additional heat generated by the fetus and placenta is effectively transferred to the environment and tolerable heat load is maintained. However, in hyperthermic environmental conditions, thermoregulatory mechanisms such as decreasing feed intake, and maternal evaporative and respiratory heat loss strategies, which rely on a temperature or humidity gradient, become compromised, maternal and fetal core-body temperatures become elevated (Hahn 1999). Modest increases in maternal core-body temperature of approximately 0.5–1.0°C for prolonged periods during mid-gestation are associated with placental insufficiency and intrauterine growth restriction (PI-IUGR) as reflected by 30–50% reductions in placental mass and up to 50% reduction to fetal weight near term (Leos et al. 2010; Limesand et al. 2006).

The mammalian fetus relies extensively on the availability of glucose and oxygen for growth (Owens 1991). PI-IUGR is characterized by an asymmetrical growth pattern (Galan et al. 1999) in which brain growth and nervous tissue function, which absolutely require glucose, are protected at the expense of somatic growth as reflected by increased fetal skull to abdominal diameter ratio, decreased fetal limb length, decreased skeletal muscle mass, and liver mass. Glucose transporter isoform GLUT-1 mRNA expression is increased in the brain of the PI-IUGR sheep fetus (Sadiq et al. 1999) while glucose utilization capacity is reduced in peripheral tissues. Fetal hypoglycemia and hypoxia both of which are present in the heat stress-induced PI-IUGR fetus are potent stimuli for fetal norepinephrine secretion from the chromaffin cells of the fetal adrenal medulla (Cohen et al. 1991). These cells become functional during mid-gestation (Comline and Silver 1966) and secrete predominantly norepinephrine due to relatively low fetal

expression, of the enzyme phenylethanolamine N-methyltransferase (PNMT) which converts norepinephrine to epinephrine (Adams and McMillen 2000).

Norepinephrine is 4 to 5-fold elevated in the heat-stressed fetal sheep which is both hypoglycemic and hypoxic (Limesand et al. 1984). In the PI-IUGR sheep fetus, norepinephrine plays a major role in nutrient distribution (Green et al. 2011) by mediating widespread glucose sparing effects to promote fetal survival via three routes by; (1) increasing fetal hepatic gluconeogenic capacity, (2) mobilization of fuels such as fatty acids and amino acids that can be metabolized peripherally in lieu of glucose, and (3) suppressing insulin sercretion. Insulin is the major anabolic hormone that coordinates fetal nutrient availability with fetal growth (Gluckman and Liggins 1984). Fetal pancreatic ß-cells are nutrient sensing cells that secrete insulin in response to increases in plasma concentrations of glucose and amino acids (Fowden 1992). Catecholamines increase hepatic gluconeogenic capacity, which is associated with up-regulation of mRNA of key gluconeogenic enzymes phosphoenolpyruvate carboxy kinase (PEPCK), and glucose -6-phosphatase (G6P) as well as increased mRNA expression of peroxisome proliferator-activated receptor-γ coactivator-1α increased phosphorylation of cAMP response element binding protein (Thorn et al. 2009). Reductions in fetal glucose oxidation rates further promote gluconeogenesis by increasing lactate availability as a substrate for hepatic gluconeogenesis (Yates et al. 2011). Catecholamines bind β-adrenergic receptors on the plasma membrane of adipose cells and initiate intracellular signaling cascades that result in activation of hormone-sensitive lipase and mobilization of fatty acids. Chronic exposure to catecholamines upregulates mRNA expression of the β2 adrenergic recepetor isoform and leads to adrenergic desensitization of perirenal adipose tissue in the fetal sheep and this defect persists postnatally leading to metabolic complications, excess fat accumulation, and unfavorable body composition. Norepinephrine suppresses fetal insulin secretion by binding to adrenergic receptor alpha-2 isoforms which are coupled to G-protein signaling pathways that suppress insulin secretion by decreasing intracellular cyclic AMP and/or calcium. Chronically elevated norepinephrine, as measured in the heat stress-induced PI-IUGR sheep fetus, is associated with increased mRNA expression of adrenergic receptor isoforms alpha1D, alpha2A, and alpha2B (Leos et al. 2010) explaining persistent impairment fetal β-cell function (Green et al. 2010). Furthermore, β-cell replication is diminished and therefore β-cell mass is reduced in PI-IUGR sheep fetuses (Limesand et al. 2005). Additionally, mRNA expression of insulin receptor (Thorn 2009) and glucose transporter isoforms GLUT-1 and GLUT-4 (Hay 2006) were found to be increased in the skeletal muscle of PI-IUGR sheep but intermediate insulin signaling elements phosphoinositide-3 kinase (p85) and protein kinase B (Akt2) were decreased (Thorn et al. 2009). Glucose utilization rates were found to be increased along with insulin sensitivity in fetal sheep with PI-IUGR (Limesand et al. 2007). This fetal programing adaptation which has been found to persist postnatally, may partially explain the observed phenomenon of “catch up” growth in PI-IUGR offspring.

While the metabolic adaptations described elsewhere by the frugal phenotype or thrifty phenotype may be advantageous for fetal survival in heat stress-induced

PI-IUGR, these adaptations have detrimental effects postnatally when nutrients and oxygen are no longer restricted. In this case animal exhibits "catch-up" growth and tends to accumulate disproportionally large amounts of fat compared to lean soft tissue which translates to lower carcass quality from a production standpoint. In summary, a better understanding of the genes affected by heat stress and the mechanisms by which their expression affects fetal and postnatal growth will elucidate opportunities improve practices to improve thermal tolerance and production in livestock.

References

Adams MB, McMillen IC (2000) Actions of hypoxia on catecholamine synthetic enzyme mRNA expression before and after development of adrenal innervation in the sheep fetus. J Physiol 529(3):519–531

Ahmed A, Dunk C, Ahmad S, Khaliq A (2000) Regulation of placental vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) and soluble Flt-1 by oxygen–a review. Placenta 21:S16–S24

Alexander G, Williams D (1971) Heat stress and development of conceptus in domestic sheep. J Agri Sci 76:53–72

Akerfelt MD, Trouillet V, Mezger , Sistonen L (2007) Heat shock factors at a crossroad between stress and development. Ann N Y Acad Sci 1113:15–27

Amici C, Sistonene L, Gabriella Santoro M, Morimoto RI (1992) Antiproliferative prostaglandins activate heat shock transcription factor. Proc Natl Acad Sci 89:6227–6231

Ansari T, Fenlon S, Pasha S (2003) Morphometric assessment of the oxygen diffusive conductance in placentae from pregnancies complicated by intra-uterine growth restriction. Placenta 24:618–626

Battaglia FC, Meschia G (1978) Principal substrates of fetal metabolism. Physiol Rev 58(2): 499–527

Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS (1993) Fetal nutrition and cardiovascular disease in adult life. Lancet 341:938–941

Bauman DE, Currie WB (1980) Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis. J Dairy Sci 63:1514–1529

Bell AW, Ehrhardt RA (2002) Regulation of placental nutrient transport and implications for fetal growth. Nutr Res Rev 15:211–230

Bell AW, McBride BW, Slepetis R, Early RJ, Currie WB (1989) Metabolites conceptus growth and maternal plasma hormones and chronic heat stress and prenatal development in sheep: I. J Anim Sci 67:3289–3299

Berman A (2004) Tissue and external insulation estimates and their effects on prediction of energy requirements and of heat stress. J Dairy Sci 87(5):1400–1412

Berman A (2005) Estimates of heat stress relief needs for Holstein dairy cows. J Anim Sci 83:1377–1384

Blackshaw JK, Blackshaw AW (1994) Heat stress in cattle and the effect of shade on production and behavior: a review. Aust J Exp Agric 34:285–295

Bligh J (1976) Introduction to acclimatory adaptation-including notes on terminology. In: Bligh J, Cloudsley-Thompson JL, Macdonald AG (eds) Environmental physiology of animals. Wiley, NY, pp 219–229

Block J, Chase CC, Hansen PJ (2002) Inheritence of resistance of bovine preimplantation embryos to heat shock: relative importance of the maternal versus paternal contribution. Mol Reprod Dev 63:32–37

Bohmanova J, Misztal I, Tsuruta S, Norman HD, Lawlor TJ (2006) Short communication: genotype by environment interaction due to heat stress. J Dairy Sci 91:840–846

Brouk MJ, Smith JF, Harner JP (2003) Effect of sprinkling frequency and airflow on respiration rate, body surface temperature and body temperature of heat stressed dairy cattle. In: Fifth international dairy housing proceedings. ASAE, Fort Worth, TX 29–31 Jan 2003, pp 263–268

Buckley BA, Hofmann GE (2002) Thermal acclimation changes DNA-binding activity of heat shock factor 1 (HSF1) in the goby Gillichthys mirabilis: implications for plasticity in the heat-shock response in natural populations. J Exper Biol 205:3231–3240

Carper SW, Duffy JJ, Gerner EW (1987) Perspectives in cancer: heat shock proteins in thermotolerance and other cellular processes. Cancer Res 47:5249–5255

Cerón-Muñoz M, Tonhati H, Costa CN, Rojas-Sarmiento D, Echeverri DM (2004) Factors that cause genotype by environment interaction and use of a multiple-trait herd-cluster model for milk yield of Holstein cattle from Brazil and Colombia. J Dairy Sci 87:2687–2692

Chan EKF, Nagaraj SH, Reverter A (2010) The evolution of tropical adaptation: comparing taurine and zebu cattle. Anim Genet 10:1365–2052

Charmandari E, Tsigos C, Chrousos G (2005) Endocrinology of the stress response. Annu Rev Physiol 67:259–284

Christenson RK, Prior RL (1978) Uterine blood flow and nutrient uptake during late gestation in ewes with different number of fetuses. J Anim Sci 46:189–200

Cohen WR, Piasecki GJ, Cohn HE, Susa JB, Jackson BT (1991) Sympathoadrenal responses during hypoglycemia, hyperinsulinemia, and hypoxia in the ovine fetus. AJP Endo 261(1): 95–102

Collier RJ, Eley RM, Sharma AK, Pereira RM, Buffington DE (1981) Shade management in subtropical environment for milk yield and composition in Holstein and Jersey cows. J Dairy Sci 64:844–849

Collier RJ, Doelger SG, Head HH, Thatcher WW, Wilcox CJ (1982) Effects of heat stress during pregnancy on maternal hormone concentrations, calf birth weight and postpartum milk yield of Holstein cows. J Anim Sci 54:309

Collier RJ, Baumgard LH, Lock AL, Bauman D (2005) Physiological limitations, nutrient partitioning. In: Sylvester-Bradley R, Wiseman J (eds) Yields of farmed species: constraints and opportunities in the 21st Century. pp 351–377

Collier RJ, Dahl GE, VanBaale MJ (2006a) Major advances associated with environmental effects on dairy cattle. J Dairy Sci Centenial 89:1244–1253

Collier RJ, Collier RP, Rhoads , Baumgard LH (2008a) Invited review: genes involved in the bovine heat stress response. J Dairy Sci 91(2):445–454

Collier RJ, Miller MA, McLaughlin CL, Johnson HD, Baile CA (2008b) Effects of Recombinant Bovine Somatotropin (rbST) and season on plasma and milk insulin-like growth factors I (IGF-I) and II (IGF-II) in lactating dairy cows. Domest Anim Endocrinol 35:16–23

Collier RJ, Stiening CM, Pollard BC, VanBaale MJ, Baumgard LH, Gentry PC, Coussens PM (2006b) Use of gene expression microarrays for evaluating environmental stress tolerance at the cellular level in cattle. J Anim Sci 84:1–13

Comline RS, Silver M (1966) Development of activity in the adrenal medulla of the foetus and new-born animal. British Med Bulletin 22(1):16–20

Da Silva RG, La Scala Jr N, Tonhati H (2003) Radiative properties of the skin and hair coat of cattle and other animals. Trans ASAE 46(3):913–918

De Vrijer B, Regnault TRH, Wilkening RB, Meshia G, Battaglia FC (2004) Placental uptake and transport of ACP, a neutral nonmetabolizable amino acid in an ovine model of fetal growth restriction. Am J Physiol Endocrinol Metab 287:1114–1124

Drake AJ, Walker BR (2004) The intergenerational effects of fetal pro- gramming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. J Endocrinol 180:1–16

Dutt RH (1963) Critical period for early embryo mortality in ewes exposed to high ambient temperatures. J Anim Sci 22:713

Edwards JL, Ealy AD, Monterroso VH, Hansen PJ (1997) Ontogeny of temperature-regulated heat shock protein 70 synthesis in preimplantation bovine embryos. Mol Reprod Dev 48: 25–33

Finch VA (1985) Comparison of non-evaporative heat transfer in different cattle breeds. Aust J Agric Res 36:497–508

Fleshner M, Johnson JD (2005) Endogenous extra-cellular heat shock protein 72: releasing signal(s) and function. Int J Hyperthermia 21:457–471

Fowden AL (1992) The role of insulin in fetal growth. Early Hum Dev 29(1–3):177–181

Fregley MJ (1996) Adaptations: some general characteristics. In: Fregley MJ, Blatteis CM (eds) Handbook of physiology, section 4: environmental physiology. Oxford University Press, Oxford, pp 3–15

Galan HL, Hussey MJ, Barbera A, Ferrazzi E, Chung M, Hobbins JC, Battaglia FC (1999) Relationship of fetal growth to duration of heat stress in an ovine model of placental insufficiency. Amer J Ob Gyn 180:1278–1282

Gaughan JB, Bonner S (2009) Hsp70 expression in cattle exposed to hot climatic conditions. In: Proceedings the 4th international congress on stress responses in biology and medicine, Sapporo Japan, PP 231

Garrett AT, Goosens NG, Rehrer NG, Patterson MJ, Cotter JD (2009) Induction and decay of short-term heat acclimation. Eur J Appl Physiol 107:659

Gebremedhin KG, Porter WP, Cramer CO (1983) Quantitative analysis of the heat exchange through the fur layer of Holstein calves. Trans ASAE 26(1):188–193

Gebremedhin KG, Porter WP, Warner RG (1984) Heat flow through pelage of calves—a sensitivity analysis. Trans ASAE 27(4):1140–1143

Gebremedhin KG, Hillman PE, Lee CN, Collier RJ (2007) Sweating rate of dairy cows under shade and sunny environments. ASABE Paper No. 074083, presented at the 2007 ASABE 100th annual international meeting, Minneapolis Convection Center, Minneapolis, Minnesota, pp 17–20

Gebremedhin KG, Hillman PE, Lee CN, Collier RJ, Willard ST, Arthington J, Brown-Brandl TM (2008) Sweating rates of dairy cows and beef heifers in hot conditions. Trans ASABE 51(6):2167–2178

Gebremedhin KG, Lee CN, Hillman PE, Collier RJ (2010) Physiological responses of dairy cows during extended solar exposure. Trans ASABE 53(1):239–247

Gebremedhin KG, Lee CN, Hillman PE, Brown-Brandl TM (2011) Body temperature and behavioral activities of four breeds of heifers in shade and full sun. App Eng J Agri ASABE 27(6): 999–1006

Gluckman PD, Liggins GC (1984) Regulation of fetal growth. In: Beard RW, Nathanielsz PW (eds) Fetal Physiology and Medicine: the basis of perinatology, 2nd edn, vol VI. Butterworth, London, pp 511–557

Grazul-Bilska AT, Borowicz PP, Johnson ML, Minten MA, Bilski JJ, Wroblewski R, Redmer DA, Reynolds LP (2010) Placental development during early pregnancy in sheep: vascular growth and expression of angiogenic factors in maternal placenta. Reproduction 140(1): 165–174

Grazul-Bilska AT, Johnson ML, Borowicz PP, Minten M, Bilski JJ, Wroblewski R, Velimirovich M, Coupe LR, Redmer DA, Reynolds LP (2011) Placental development during early pregnancy in sheep: cell proliferation, global methylation, and angiogenesis in the fetal placenta. Reproduction 141:529–540

Green AS, Rozance PJ, Limesand SW (2010) Consequences of a compromised intrauterine environment on islet function. J Endocrinol 205(3):211–224

Green AS, Macko AR, Rozance PJ, Yates DT, Chen X, Hay WW Jr, Limesand SW (2011) Characterization of glucose-insulin responsiveness and impact of fetal number and sex difference on insulin response in the sheep fetus. Am J Physiol Endocrinol Metab 300(5): 817–823

Guzhova IK, Kislyakova O, Moskaliova I, Fridlanskaya M, Tytell M, Cheetham B (2001) In vitro studies show that Hsp70 can be released by glia and that exogenous Hsp70 can enhance neuronal stress tolerance. Brain Res 914:66–73

Habib KE, Gold PW, Chrousos GP (2001) Neuroendocrinology of stress. Endocrinol Metab Clin North Am 30:695–728

Hafez SA (1964) Effects of high temperature on reproduction. Int J Biometeor 7:223

Hafez SA, Borowicz P, Reynolds LP, Redmer DA (2010) Maternal and fetal microvasculature in sheep placenta at several stages of gestation. J Anatomy 216:292–300. doi:10.1111/j.1469-7580.2009.01184.x

Hales JR, Fawcett AA, Bennett JW, Needham AD (1978) Thermal control of blood flow through capillaries and arteriovenous anastomoses in skin of sheep. Pflugers Arch 378:55–63

Hahn GL (1999) Dynamic responses of cattle to thermal heat loads. J Anim Sci 77(2):10–20

Hansen PJ (2004) Physiological and cellular adaptations of zebu cattle to thermal stress. Anim Reprod Sci 82–83:349–360

Hay WW (2006) Placental-fetal glucose exchange and fetal glucose metabolism. Trans Am Clin Climatol Assoc 117:321–339

Hayes B, Bowman P, Chamberlain A, Goddard M (2009) A validated genome-wide association study to breed cattle adapted to an environment altered by climate change. PLoS ONE 4:6676

Hillman PE, Gebremedhin KG, Parkhurst AM, Fuquay J, Willard ST (2001) Evaporative and convective cooling of cows in a hot and humid environment. In livestock environment VI: Proceedings of the 6th International Symposium, ASABE, St. Joseph, MI, pp 343–350

Hillman PE, Lee CN, Willard ST (2005) Thermoregulatory responses associated with lying and standing in heat-stressed dairy cows. Trans ASAE 48(2):795–801

Horowitz M (2002) From molecular and cellular to integrative heat defense during exposure to chronic heat. Comp Biochem Physiol A Mol Integr Physiol 131(3):475–483

Horowitz M (2007) Heat acclimation and cross-tolerance against novel stressors: genomic-physiological linkage. Prog Brain Res 162:373–392

Horowitz M, Assadi H (2010) Heat acclimation-mediated cross-tolerance in cardioprotection: Do HSP70 and HIF-1a play a role? Ann N Y Acad Sci 1188:199–206

Horowitz M, Eli-Berchoer L, Wapinski I, Friedman N, Kodesh E (2004) Stress-related genomic responses during the course of heat acclimation and its association with ischemic-reperfusion cross-tolerance. J Appl Physiol 97:1496–1507

Horowitz M, Robinson SD (2007) Heat shock proteins and the heat shock response during hyperthermia and its modulation by altered physiological conditions. Prog Brain Res 162:433–436

Ianaro A, Ialenti A, Maffia P, Di Meglio P, Di Rosa M, Santoro MG (2003) Anti-Inflammatory Activity of 15-Deoxy-$D^{12,14}$-PGJ_2 and 2-Cyclopenten-1-one: Role of the Heat Shock Response. Mol Pharmacol 64:85–93

Ireland HE, Leoni F, Altaie O, Birch CS, Coleman RS, Hunter-Lavin C, Williams JJH (2007) Measuring the secretion of heat shock proteins from cells. Methods 43(176):183

Jansson T, Scholtbach V, Powell TL (1998) Placental transport of leucine and lysine is reduced in intrauterine growth restriction. Pediatr Res 44:532–537

Johnson HD, Vanjonack WJ (1976) Effects of environmental and other stressors on blood hormone patterns in lactating animals. J Dairy Sci 59:1603–1617

Jousan FD, Hansen PJ (2004) Insulin-like growth factor-I as a survival factor for the bovine preimplantation embryo exposed to heat shock. Biol Reprod 71(5):1665–1670

Kamwanja LA, Chase CC, Gutierrez JA, Guerriero V, Olson TA, Hammond AC (1994) Responses of bovine lymphocytes to heat shock as modified by breed and antioxidant status. J Anim Sci 72:438–444

Kimmel E, Arkin H, Broday D, Berman A (1991) A model of evaporative cooling in a wetted hide. J Agric Eng Res 49(3):227–241

Kingdom JCP, Kaufmann P (1997) Oxygen and placental villous development: origins of fetal hypoxia. Placenta 18:613–621

Kowalski GJ, Mitchell JW (1979) An analytical and experimental investigation of the heat transfer mechanism within fibrous media, ASME, New York, 79-WA/HT-40
Kregel KC (2002) Molecular biology of thermoregulation invited review: heat schock proteins: modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol 92:2177–2186
Kristensen TN, Løvendahl P, Berg P, Loeschcke V (2004) Hsp 72 is present in plasma from Holstein-Friesian dairy cattle, and the concentration level is repeatable across days and age classes. Cell Stress Chaperones 9:143–149
Leiser R, Krebs C, Klisch K, Ebert B, Dantzer V, Schuler G, Hoffmann B (1997) Villosity and microvasculature of the bovine placentome in the second half of gestation. J Anat 191: 517–527
Leos RA, Anderson MJ, Chen X, Pugmire J, Anderson KA, Limesand SW (2010) Chronic exposure to elevated norepinephrine suppresses insulin secretion in fetal sheep with placental insufficiency and intrauterine growth restriction. American J Physiol 298(4):770–778
Lillehammer M, Hayes BJ, Meuwissen THE, Goddard ME (2009) Gene by environment interactions for production traits in Australian dairy cattle. J Dairy Sci 92:2008–4017
Limesand SW, Regnault TRH, Hay WW (2004) Characterization of glucose transporter 8 (GLUT8) in the ovine placenta of normal and growth restricted fetuses. Placenta 25(1):70–77
Limesand SW, Jensen J, Hutton JC, Hay WW (2005) Diminished beta-cell replication contributes to reduced beta-cell mass in fetal sheep with intrauterine growth restriction. Am J Physiol Regul Integr Comp Phyiol 288:1297–1305
Limesand SW, Rozance PJ, Zerbe GO, Hutton JC, Hay WW (2006) Attenuated insulin release and storage in fetal sheep pancreatic islets with intrauterine growth restriction. Endocrinology 147:1488–1497
Limesand SW, Rozance PJ, Smith D, Hay WW Jr (2007) Increased insulin sensitivity and maintenance of glucose utilization rates in fetal sheep with placental insufficiency and intrauterine growth restriction. Am J Physiol Endocrinol Metab 293:1716–1725
Maia ASC, daSilva RG, Loureiro CMB (2005) Sensible and latent heat loss from the body surface of Holstein cows in a tropical environment. Intl J Biometeor 50(1):17–22
Maia ASC, daSilva RG, Loureiro CMB (2008) Latent heat loss of Holstein cows in a tropical environment: a prediction model. R Bras Zootec 37(10):1806–9290
Manalu W, Johnson HD, Li R, Becker BA, Collier RJ (1991) Assessment of thermal status of somatotropin-injected lactating Holstein cows maintained under controlled-laboratory thermoneutral, hot and cold environments. J Nutr 121:2006–2019
McArthur AJ (1987) Thermal interaction between animal and microclimate–a comprehensive model. J Theor Biol 126(2):203–238
McDowell RE (1958) Physiological approaches to animal climatology. J Hered 49:52–61
Moen AN (1973) Wildlife ecology- an analytical approach. Freeman and Company WH, San Francisco, p 458
Magee DA, Meghen C, Harrison S, Troy CS, Cymbron T, Gaillard C, Morrow A, Maillard CG, Bradley DG (2002) A partial African ancestry for the creole cattle populations of the Caribbean. J Hered 93:429–432
Maloyan A, Palmon A, Horowitz M (1999) Heat acclimation increases basal HSP72 level and alters its produciton dynamics during heat stress. Am J Physiol Regul Integr Comp Physiol 276:1506–1515
Maloyan A, Eli-Berchoer L, Semenza GL, Gerstenblith G, Stern GD, Horowitz M (2005) HIF-1a-targeted pathways are activated by heat acclimation and contribute to acclimation-ischemic cross-tolerance in the heat. Physiol Genomics 23:79–88
Mossman HW (1987) Vertebrate fetal membranes. Rutgers University Press, New Brunswick
Myers SA, Sparks JW, Makowski EL, Meschia G, Battaglia FC (1982) Relationship between placental blood flow and placental and fetal size in guinea-pig. Am J Physiol 24:404–409
Norberg S, Powell TL, Jansson T (1998) Intrauterine growth restriction is associated with a reduced activity of placental taurine transporters. Pediatr Res 44:233–238

Olson AL, Pessin JE (1996) Structure, function, and regulation of the mammalian facilitative glucose transporter gene family. Annu Rev Nutr 16:235–256
Olson TA, Chase CC, Lucena C, Godoy E, Zuniga A, Collier RJ (2006) Effect of hair characteristics on the adaptation of cattle to warm climates. 8th World congress on genetics applied to livestock production, Belo Horizonte, MG, Brasil, 13–18 Aug 2006
Owens JA (1991) Endocrine and substrate control of fetal growth: placental and maternal influences and insulin-like growth factors. Reprod Fertil Dev 3(5):501–517
Paula-Lopes FF, Chase CC, Al-Katanani YM, Krininger CE, Rivera RM, Tekin S, Majewski AC, Ocon OM, Olson TA, Hansen PJ (2003) Genetic divergence in cellular resisitance to heat shock in cattle: differences between breeds developed in temperate versus hot climates in responses of preimplantation embryos, reproductive tract tissues and lymphocytes to increased culture temperatures. Reprod 125:285–294
Power GG (1989) Biology of temperature: the mammalian fetus. J Dev Physiol 12:295–304
Ravagnolo O, Misztal I, Hoogenboom G (2000) Genetic component of heat stress in dairy cattle, development of heat index function. J Dairy Sci 83:2120–2125
Regnault TRH, Friedman JE, Wilkening RB, Anthony RV, Hay WW (2005) Fetoplacental transport and utilization of amino acids in IUGR—a review. Placenta, pp 52–62
Regnault TRH, Orbus RJ, De Vrijer B, Davidsen ML, Galan HL, Wilkening RB, Anthony RV (2002) Placental expression of VEGF, PlGF and their receptors in a model of placental insufficiency–intrauterine growth restriction (PI-IUGR). Placenta 23(2–3):132–144
Regnault TRH, de Vrijer B, Galan HL, Davidsen ML, Trembler KA, Battaglia FC, Wilkening RB, Anthony RV (2003) The relationship between transplacental O2 diffusion and placental expression of PlGF, VEGF and their receptors in a placental insufficiency model of fetal growth restriction. J Physiol 550:641–656. doi:10.1113/jphysiol.2003.039511
Regnault TRH, de Vrijer B, Galan HL, Wilkening RB, Battaglia FC, Meschia G (2007) Development and mechanisms of fetal hypoxia in severe fetal growth restriction. Placenta 28:714–723
Reynolds LP, Borowicz PP, Vonnahme KA (2005) Placental angiogenesis in sheep models of compromised pregnancy. J Physiol 565:43–58
Rhoads ML, Rhoads RP, VanBaale MJ, Collier RJ, Sanders SRS, Weber WJ, Crooker BA, Baumgard LH (2009) Effects of heat stress and plane of nutrition on lactating Holstein cows: I. Production, metabolism, and aspects of circulating somatotropin. J Dairy Sci 92:1986–1997
Roberts MF, Wenger CB, Stolwijk JAJ, Nadel ER (1977) Skin blood flow and sweating changes following exercise training and heat acclimatization. J Appl Physiol 43:133–137
Ross JC, Fennessey PV, Wilkening RB, Battaglia FC, Meschia G (1996) Placental transport and fetal utilization of leucine in a model of fetal growth retardation. Am J Physiol Endocrinol Metab 270:491–503
Sadiq HF, Das UG, Tracy TF, Devaskar SU (1999) Intra-uterine growth restriction differentially regulates perinatal brain and skeletal muscle glucose transporters. Brain Res 823(1–2):96–103
Sarge KD, Murphy SP, Morimoto RI (1993) Activation of heat shock gene transcription by heat shock factor 1 involves oligomerization, acquisition of DNA-binding activity, and nuclear localization and can occur in the absence of stress. Mol Cell Biol 13:1392–1407
Scott GH (1981) What is animal stress and how is it measured? J Anim Sci 52:150
Shamovsky I, Nudler E (2008) New insights into the mechanism of heat shock response activation. Cell Mol Life Sci 65:855–861
Silanikove N, Shapiro F, Shinder D (2009) Acute heat stress brings down milk secretion in dairy cows by up-regulating the activity of the milk-borne negative feedback regulatory system. BMC Physiol 9(13):
Sonna LA, Fujita J, Gaffin SL, Lilly CM (2002) Molecular biology of thermoregulation invited review: effects of heat and cold stress on mammalian gene expression. J Appl Physiol 92:1725–1742
Stowell RR (2000) Heat stress relief and supplemental cooling. In: Dairy housing and equipment systems conference proceedings of the Natural Resource, Agriculture, and Engineering

Service (NRAES). Cornell University, Ithaca, New York, Department of Agricultural and Biological Engineering, pp 129

Straus DS, Glass CK (2001) Cyclopentenone prostaglandins: new insights on biological activities and cellular. Med Res Rev 21:185–210

Thorn SR, Regnault TRH, Brown LD, Rozance PJ, Keng J, Roper M, Wilkening RB, Hay WW, Friedman JE (2009) Intrauterine growth restriction increases fetal hepatic gluconeogenic capacity and reduces messenger ribonucleic acid translation initiation and nutrient sensing in fetal liver and skeletal muscle. Endocrinol 150(7):3021–3030

Thureen PJ, Trembler KA, Meschia G, Makowski EL, Wilkening RB (1992) Placental glucose transport in heat-induced fetal growth retardation. Am J Physiol Regul Integr Comp Physiol 263:578–585

Tytell M (2005) Release of heat shock proteins (Hsps) and the effects of extracellular Hsps on neural cells and tissues. Int J Hyperthermia 21:445–455

Voellmy R, Boellmann F (2007) Chaperone regulation of the heat shock protein response. Adv Exp Med Biol 594:89–99

Xu Q, Ganju L, Fawcett TW, Holbrook NJ (1996) Vasopressin-induced heat shock protein expression in renal tubular cells. Lab Invest 74:178–187

Yates DT, Green AS, Limesand SW (2011) Catecholamines mediate multiple fetal adaptations during placental insufficiency that contribute to intrauterine growth restriction: lessons from hyperthermic sheep. J Pregnancy 11:740408

Yousef MK (1984) Stress physiology in livestock, Vol I, basic principles. CRC Press Inc, Boca Raton, p 217