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Stress biomarkers and proteomics alteration to thermal stress in ruminants: A review

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ABSTRACT

Heat stress may adversely affect physiochemical and immune responses of livestock and alter biological functions. The comfort or thermoneutral zone for livestock, which has long been a subject of research, mainly depends on species, breed, and health. Heat stress is associated with impaired livestock productivity due to reductions in feed intake, growth rates and immunity and changes in blood constituents and biological pathways. In ruminants, elevated temperatures have deleterious consequences on protein synthesis. Exposure of ruminant animals to elevated temperatures may induce release of heat shock proteins (HSPs); HSPs usually enter the blood circulation during tissue damage and causes cell necrosis or death. Additionally, hyperthermia is associated with augmented production of cellular reactive oxygen species (ROS), which cause protein degradation and further decrease protein synthesis by preventing protein translation. Moreover, it has been suggested that high environmental temperatures lead to increased inflammatory signalling in tissues via activation of the nuclear factor kappa B (NF-κB) and tumor necrosis factor alpha (TNF-α) pathways as well as via alteration of skin colour gene (melanocortin 1 receptor (MC1R) and premelanosome protein (PMEL)) expression. Previous proteomics analyses have suggested that heat stress can reduce adenosine triphosphate (ATP) synthesis, alter gluconeogenesis precursor supply, and induce lipid accumulation in the liver with subsequent disturbance of liver structure. This review focuses on the scientific evidence regarding the impact of heat stress on immune and inflammatory responses, antioxidant status, stress biomarkers, skin colour gene (PMEL and MC1R) expression and proteomic profiles in ruminants.

1. Introduction

Global warming is a major threat not only for human health worldwide but also for livestock production. In any given region, environmental temperatures fluctuate considerably throughout the year by 10–44 °C. The potential environmental heat stress has negative impacts on biochemical pathways, immune and inflammatory responses, proteomics, and physiologic and performance traits in livestock and poultry (Sheikh et al., 2017; Maibam et al., 2018; Skibiel et al., 2018; Farag and Alagawany, 2018). The majority of livestock species tolerate temperatures ranging from 16° to 25°C. Cells can respond to high environmental temperatures by producing new or constitutively stimulating molecular chaperones, such as stress-denatured proteins or heat shock proteins (HSPs), which support the production, folding and transportation of nascent proteins (Stetler et al., 2010). In addition, elevated environmental temperatures increase the production of reactive oxygen species (ROS), with subsequent induction of oxidative damage to lipids, proteins, and DNA (Maibam et al., 2018). Recently, several studies have concluded that heat stress induces oxidative damage in many livestock species (Guo et al., 2018; Maibam et al., 2018).

Heat stress becomes evident when the amount of heat generated by an animal's body exceeds the ability of the body to distribute heat to its surroundings. Such a condition is difficult to assess due to the presence of several external factors, such as temperature, humidity, sunlight, air movement, and thermal radiation. Additionally, some features of an animal, such as its species, sex, and metabolic rate, impact heat stress

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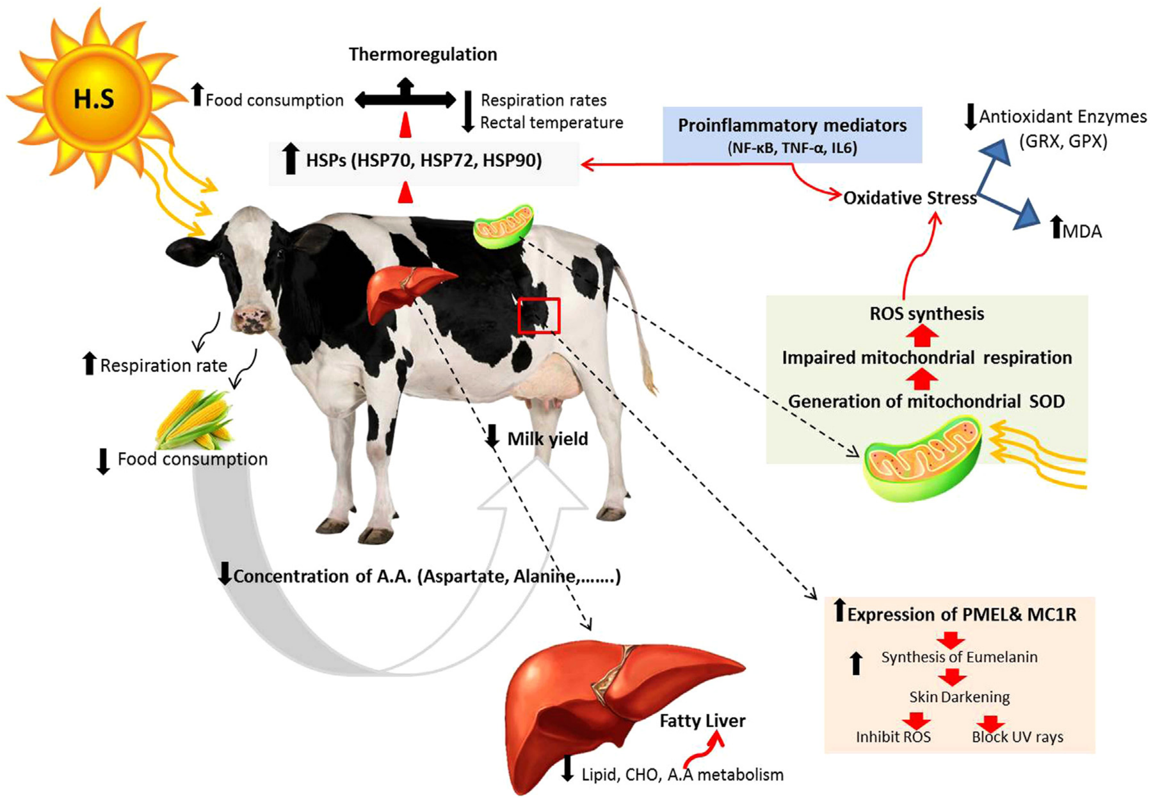

Fig. 1. Summary for heat stress adverse impact and body reactions in ruminant.

(Abdelnour et al., 2012; Daader et al., 2016; Farag and Alagawany, 2018). Heat stress can be classified into two principal classes: chronic heat stress, in which the elevation in ambient temperature continues for a long period of time (ranging from days to even weeks), allowing environmental acclimation, and acute heat stress, in which there is a rapid and brief increase in ambient temperature. These two types of heat stress are both able to stimulate numerous physiochemical responses (Fig. 1), such as depression of immune and endocrine functions, changes in blood amino acids, reductions in cellular energy bioavailability, elevations in HSP mRNA expression, and upregulation of inflammatory genes (NF-κB and TNF-α) and PMEL and MC1R, augmentation of oxidative stress and reductions in antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPx), and malondialdehyde (MDA)), subsequently disturbing intestinal cell function and structure (Chauhan et al., 2014a, 2014b, 2014c; Rathwa et al., 2017; Guo et al., 2018; Maibam et al., 2018). Furthermore, heat stress can alter the proteomic profiles of animal tissues (Skibiel et al., 2018). In the current review, the deleterious influences of heat stress on some specific variables in blood, milk and meat, such as amino acid levels, immune responses, oxidative/antioxidative status, HSP levels, cytokine levels, proteomic profiles, and inflammatory gene (TNF-α and NF-κB) and skin colour gene (PMEL and MC1R) expression, were explored in ruminants.

2. Heat stress biomarkers

2.1. Blood amino acid profiles

High environmental temperatures can affect the metabolism and nutritional status of different livestock species (Table 1). For instance, heat-stressed dairy cows fail to properly manage glucose utilization mechanisms due to the high environmental temperature (Baumgard et al., 2011). Moreover, dairy cows exposed to heat stress may reduce feed consumption and experience increased maintenance requirements and reductions in nutrient availability for milk synthesis and production (Wang et al., 2010). Furthermore, Gorniak et al. (2014) detected reduced milk yield of mid-lactation Holstein dairy cows when the temperature-humidity index (THI) was elevated above 60, while water intake rose continuously in a linear manner above a THI of 30. In addition, milk fat and milk protein content decreased linearly with increasing THI. However, Murphy et al. (1983) previously reported that increased water consumption during heat stress is accompanied by increased milk volume and cooling of the body due to lowering of rumen temperature (Bhattacharya and Warner, 1968).

Lamp et al. (2015) investigated the influences of heat stress on the biological functions of high-yielding German Holstein transition cows. The authors observed a severe significant effect of heat on water homeostasis with impairments in renal function and a powerful adrenergic response associated with a predominance of carbohydrate oxidation rather than fat catabolism. Furthermore, heat stress destroyed tissue protein, as reflected by elevations in methylhistidine, creatinine, and plasma urea concentrations. However, acute metabolic heat stress causes a lower rate of amino acid oxidation in dry cows than in cows in the post-partum stage. Cows heat-stressed for 7 d have been found to exhibit disruptions in nitrogen metabolism, nitrogenous repartition and diminished milk protein levels; however, the heat stress increases milk urea levels (Cowley et al., 2015).

Blood amino acids are responsible for the synthesis of the main constituents of milk protein in ruminant mammary glands. Numerous studies have noted marked alterations in circulating amino acids under catabolic status (Flynn et al., 2000). Recently, it was reported that amino acid levels in dairy cow plasma are altered by exposure to high environmental temperature. In dairy cows reared under heat stress, Guo et al. (2018) found significantly higher ($P < 0.05$) concentrations of total amino acids, aspartate, alanine, glutathione, threonine, and glycine than those in non-heat-stressed cows. However, Guo et al. reported higher levels of lysine under normal conditions than under heat-stressed conditions ($P < 0.05$). Such recorded elevations in alanine

Table 1
Impacts of heat stress on animals.

Items	Species	Environmental Heat stress	Main findings	References
1. Blood amino acids profile	Holstein-Friesian cows	Heat-stressed cows (TN-R) for 7 d.	● Disturbance in metabolism of nitrogen and incentive nitrogenous repartition. ● Diminishing in protein percentage in milk ● Increase milk level of urea.	Cowley et al. (2015)
	Holstein cows	Sino-farm (Beijing, China) Summer environment.	● Significant increase in concentrations of total amino acids, aspartate, alanine, glutathione, threonine, and glycine.	Guo et al. (2018)
2. Heat shock proteins family	Sheep	28–40 °C and 40–50% relative humidity for 2 wk.	● HSF1and HSP70 from skeletal muscles were increased by 1.3 and 3.5-fold under thermal stress.	–
	Pig	Continuous high ambient temperature (35 °C ± 1 °C).	● HSP70 expression in pigs muscle was increased significantly.	Pearce et al. (2013a)
	Sheep	Temperature range from 18 °C to 43 °C.	● Increased expression of HSP70 in mononuclear blood cells.	Romero et al. (2013)
	Beef steers	With and without shade for 120 days.	● Greater expression of HSP70 in adipocytes.	DiGiacomo et al. (2014)
	Sheep	28°C-40°C and 40%-50% relative humidity for 1 wk.	● Marked substantial fluctuations in HSP90 overall expression in skeletal muscle.	Chauhan et al. (2014c)
	Beef cattle	Mild chronic thermal stress with and without shade for 120 days.	● The expression of HSP90 in adipocytes attained from beef cattle muscle reared under mild chronic thermal stress was reduced when animals were delivered with shade.	DiGiacomo et al. (2014)
	Beef cattle		● Sahiwal (*Bosindicus*) breed of cattle expressed higher HSP90 expression compared to Frieswal (*Bosindicus* × *Bostaurus*) cattle, which adjusted their body's temperature and enhanced the cell survival rates along with high temperature surroundings.	Deb et al. (2014)
	Ewes	28°C–40 °C and relative humidity ranged between 40%–50% for one week.	● An increment in both tumor necrosis factor alpha (TNF-α) mRNA of tissue (5.7-fold; $P = 0.013$), and nuclear factor kappa B (NF-κB) of skeletal muscle (5.2-fold; $P = 0.005$). ● Skeletal muscle expression of TNF-α was augmented and joined by increased plasma advanced oxidation protein products (AOPP), which resulted in access production of oxidative stress.	Chauhan et al. (2014c)
3. Inflammatory gene expression (nuclear factor kappa B (NF-κB) and tissue tumor necrosis factor α (TNF-α))	Pigs	35 °C for 1 or 3 days	● Conveyed that even with increased ROS and TNF-α, pig's muscle which has been exposed to elevated environmental temperature for one and three days showed a conflicting signs of fluctuations related to oxidative injury and NF-κB signaling in skeletal muscle.	Montilla et al. (2014)
		Chronic heat stress.	● Leads to detrimental pro-inflammatory responses.	Celi (2011b)
		To one or three days of thermal stress.	● Elevated protein amount of TNF-α was indicated in semitendinosus pigs red muscle.	Montilla et al. (2014)
	Ruminants		● Exaggerated ROS production can discompose the enzymes of antioxidant defenses, bringing in oxidative stress.	Celi (2011a)
	poultry	Acute heat stress.	● Severe heat stress induces generation of mitochondrial superoxide in tissues of skeletal muscles, which resulted in oxidative impairment to the lipid and proteins synthesis in mitochondria.	Mujahid et al. (2005)
4. Oxidative stress markers	Cattle		● Evaluated the oxidative stress markers (GRx, GPx and ROS) in cells of cattle's skin with various coat colors; in cold and heat ambient temperature, significant higher levels of ROS synthesis in Zebu and Karan Fries cattle. ● However, ROS concentration in the tissue of skin showed significant ($P < 0.05$) increase in Karan Fries than Zebu cattle through hot environmental period.	Maibam et al. (2018)
	Gill tissues of the Antarctic polar bivalve *Laternula elliptica*		● Mitochondrial respiration and the subsequent ROS generation were adversely affected the elevated temperatures.	Heise et al. (2003)
	Bovine	(41 °C) on granulosa cell functions at 24 h and 48 h exposure compared to the control cultured at 37 °C.	● Studied the impact of high environmental temperature on cultivated bovine granulosa cells; they concluded great expression of stress marker genes of endoplasmic reticulum (ER) namely GRP78 and GRP94 after 24 hours, and apoptotic genes namely Caspase-3 and	Alemu et al. (2018)

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Table 1 (*continued*)

Items	Species	Environmental Heat stress	Main findings	References
			Bax, along with aggregation of GRP78 protein and reduced regeneration of bovine granulosa cells. ● Altogether, thermal stress stimulate apoptosis and ROS synthesis, while it reduced cellular proliferation with subsequent activation of NRF2- induced oxidative injury and ER response in bovine granulosa cells.	
5. Antioxidants indices				
5.1. Glutathione peroxidases (GPx)	Sheep	28°-40°C and relative humidity 40%–50% for one week.	● Suggested that chronic thermal stress had a tendency to (P = 0.070) decline GPx-1 mRNA in sheep muscle.	Chauhan et al. (2014c)
	Cattle		● Reported that levels of the antioxidants enzymes (GRx and GPx) showed significant ($P < 0.05$) increase in skin during summer and winter season comparing to spring in Zebu and Karan Fries cattle. ● But, during hot environmental temperature, the levels of GRx and GPx were significantly higher in Karan Fries than Zebu cattle.	Maibam et al. (2018)
	Goat	28–46 °C.	● The levels of GRx and GPx was increased in environmental temperature equal to 46 °C as compared to 28 °C in Marwari goats	Maan et al. (2013)
	Rats	Cyclic heat stress (23 to 38 to 23 °C) for 2 h on each of seven consecutive days.	● Found that cyclic thermal stress rises the concentrations of hepatic GPx and their expression mRNA in rat.	Yun et al. (2012)
	Buffaloes and cattle	40 °C	● Reported an increment in levels of blood GRx and GPx in buffaloes and cattle reared under 40 °C.	Kumar (2005)
	Karan Fries cattle		● Elevated concentrations of oxidative stress biomarkers during thermal environmental stress designated countless generation of ROS in their skin tissues, compared to zebu cattle.	Gihan et al. (2009)
	Sheep		● Found that plasma GPx of Indian Indigenous sheep was increased (1.29) times ($p < 0.05$) during the hot season than mild season	Rathwa et al. (2017)
	Red Sokoto goats		● Reported that no change has been recorded in GPx during heat stress.	–
	Sheep	28°-40°C and relative humidity 40%–50% for one week	● Stated that the mRNA expression of muscle SOD-2 was reduced by 60% in sheep exposed to chronic high temperature (P = 0.015). It appears that continuing thermal stress resulted in reduction of the antioxidant enzymes with subsequent elevation in oxidative stress.	Chauhan et al. (2014c)
	Pigs	After 24 hours of high ambient temperature	● Augmented expression of SOD and catalase (antioxidant enzymes) was reported in red muscle of semitendinosus pigs after 24 hours of high ambient temperature, while the expression status pay back to normal levels on three days of high ambient temperature.	Montilla et al. (2014)
5.2. Superoxide dismutase(SOD)	Indian Indigenous sheep	Temperature-humidity index (THI) value of Summer and winter season were 82.55 and 59.36, respectively	● Found that plasma SOD of Indian Indigenous sheep was increased (1.46, $p < 0.05$) times during summer season than the winter season.	Rathwa et al. (2017)
	Red Sokoto goats		● Reported lower activity of SOD in red Sokoto goats reared under dry hot season.	–
	Dairy cattle	Sino-farm (Beijing, China) Summer environment.	● Heat stressed cow had greater plasma MDA concentrations (133.4%) than those in cow reared under autumn season, suggesting that thermal stress could impair immunity defense via the depletion of enzymatic antioxidants. ● The high environmental temperature inhibited the activity of antioxidant enzymes and increased lipid peroxidation in the cellular pathways.	Guo et al. (2018)
	Goats		● Higher levels of MDA during hot dry season (THI = 73–86.3) in red Sokoto goats. ● Catalase activity showed significant ($P < 0.05$) decrease in the thermal stressed goats than in those administrated L-glutamine.	–
5.3. Malondialdehyde (MDA)	Sheep	Temperature-humidity index (THI) value of summer and winter season were 82.55 and 59.36, respectively.	● However Indian Indigenous sheep showed increased level of plasma LPO (1.31 times, $p < 0.05$) during high temperature (THI value = 82.55) than in winter (THI value = 59.36) season.	Rathwa et al. (2017) McRobie et al. (2014)

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Table 1 (*continued*)

Items	Species	Environmental Heat stress	Main findings	References
	The gray squirrel (*Sciurus carolinensis*)		● Reported that Melanocortin 1 receptor (MC1R) gene has a role in pigmentation variances in mammals.	
			● MC1R allele encourages the black pigment which protects skin against UV injury.	Greave (2014)
6. Skin color genes (PMEL and MC1R)			● Premelanosome (PMEL) gen is a melanocyte protein which has a role in deposition of eumelanin.	McGlinchey et al. (2009)
	Zebu cattle		● Increased expression of color genes (PMEL and MC1R) in skin of Zebu cattle might induce higher synthesis of eumelanin in skin cells more than Karan Fries cattle. MC1R gene has a great binding capacity to ACTH and α-MSH.	Mountjoy (1994)
	Karan Fries cows		● Reported that when Karan Fries cows exposed to heat stress, they showed significant increase ($P < 0.05$) in their blood content of IL-6 (1.32 times), and significant decrease in IL-12 concentration as compared to control group.	Sheikh et al. (2017)
	Human		● IL-6 gets raised during high environmental temperature.	–
7. Interleukin	Human		● Heat stress magnifies TNF and IL-6 levels in males.	Starkie et al. (2005)
	Lactating cows		● As a result, heat-stressed cows have markedly reduced milk production throughout lactation and are more susceptible to metabolic disorders during the transition period.	(Kadzerea et al., 2002; Bernabucci et al. 2010); Tao and Dahl (2013).
	Cows		● Alters mammary gland remodeling and hepatic lipid metabolism.	do Amaral et al. (2009, 2011); Tao et al. (2011)
8. Liver proteomics	Cows	Heat stress dring dry period.	● reported an alteration in proteomics analysis and protein abundance in the liver of transitioning cows exposed to hot climate or cold environment conditions during the dry period. ● Heat-stressed cattle have impaired mitochondrial function and altered lipid, carbohydrate, and amino acid metabolism in the liver, as indicated by the top canonical pathways and biological functions identified by IPA. ● Based on differential abundance of proteins in these pathways, it seems probable that heat-stressed cows have reduced ATP synthesis, greater oxidative stress, shifts in the precursor supply for gluconeogenesis, and accumulation of the hepatic lipids in their liver that may contribute to fatty liver disease.	Skibiel et al. (2018)

levels may suggest that gluconeogenesis is reinforced under heat stress. However, the lower levels of lysine in heat stress-exposed cows could be attributed to reductions in feed intake. Moreover, the observed elevations in plasma amino acid levels in heat-stressed cows may be due to nutrient scarcity, gluconeogenesis and the ability of amino acid catabolic products to integrate into liver tissues (Stahel et al., 2014; Ai et al., 2015; Guo et al., 2018). Cowley et al. (2015) suggested that low concentrations of plasma glucose would induce more restricted consumption of amino acids to promote gluconeogenesis in heat-stressed cows, and it has been concluded that alanine signalling can adjust glycolysis and gluconeogenesis to maintain glucose synthesis throughout a period of feed restriction (Meijer, 2003). Also, the amino acid threonine has previously been implicated in immune function under heat stress conditions, as threonine levels increase in intestinal epithelial cells after heat injury and increase cell viability in a dose-dependent manner. The authors attributed the protective effects of threonine to high levels of HSP70 and HSP25 expression that stabilize the cytoskeleton and decrease apoptosis (Baird et al., 2013). Based on these findings, it could be suggested that high environmental temperatures decrease the use of amino acids in the synthesis of milk protein with implicated involvement of immune responses and gluconeogenesis.

Ghassemi Nejad et al. (2013) studied the influence of water restriction on water consumption patterns and blood and wool cortisol concentrations in heat-stressed sheep. The authors divided the animals into three groups: a group with free access to water (FAW), a group with 2 h of water restriction after feeding (2hWR) and a group with 3 h of water restriction after feeding (3hWR). The average THI was 27.9 throughout the experiment, representing heat stress conditions. Total wool cortisol concentrations were greater in the 3hWR group than in the other treatment groups. However, blood cortisol concentrations were the same in all treatments, and the data were very variable compared to those for wool cortisol. Therefore, wool cortisol could be analysed to obtain more accurate data during heat stress conditions than that provided by blood cortisol.

2.2. Milk biomarkers

Heat stress reduces milk quality and yields, causing great economic losses every year. Tian et al. (2015) and Tian et al. (2016) investigated metabolomic and lipidomic variances in milk biomarkers and metabolic pathways between heat stress-free and heat-stressed cows. The authors detected a significant correlation between heat stress biomarkers in milk and previously identified candidate heat stress biomarkers in plasma. Biomarkers including pyruvate, lactate, acetone, β-hydroxybutyrate, creatine, oleic acid, trimethylamine, lysophosphatidylcholine, linoleic acid, glucose, betaine, acetoacetate, C16 sphinganine, arachidonic acid and phosphatidylcholine were detected in plasma and milk, indicating the leakiness of the blood-milk barrier and suggesting that the levels of milk biomarkers are related to heat shock-induced metabolomic changes in the blood. Plasma lactate and pyruvate concentrations from heat-stressed and heat stress-free cows were markedly correlated with their concentrations in milk, suggesting that lactate and pyruvate are directly secreted from the blood into the milk through the mammary gland (Lehmann et al., 2013). The increased galactose-1-phosphate concentrations in milk in heat-stressed cows supports the hypothesis that leakage of galactose-1-phosphate from mammary epithelial cells into milk occurs through apoptosis. Furthermore, other evidence for mammary cell apoptosis included detection of elevated Bax, P53 protein, caspase-3, cytochrome c, caspase-9, and caspase-8 levels and reduced Bcl-2 levels in both milk and plasma of heat-stressed cows; all of these proteins are apoptosis-related molecules (Cheng et al., 2015).

Citrate in milk is utilized as a biomarker of energy balance in dairy cows and is the cause of the presence of ketone bodies in milk (Klein et al., 2013). High milk citrate levels, rather than plasma citrate levels, in heat-stressed cows indicate a disturbance in mammary function more than a disturbance in general metabolism, because the mammary epithelium is resistant to citrate leakage in both directions (Klein et al., 2013). Low concentrations of proline, isoleucine, glycine, orotate, and phosphocreatine were observed in the milk of heat-stressed cows in contrast to their upregulation in plasma, a finding that may be attributed to elevated skeletal muscle protein degradation into amino acids in plasma during heat stress (Wheelock et al., 2010). These amino acids might be the main precursors for energy production via oxidation and deamination or glucose production via gluconeogenesis (Li et al., 2015), reducing their passage into milk. The finding that urea concentrations were higher in plasma than in milk in heat-stressed dairy cows suggests that more amino acids were metabolized into urea than used to synthesize milk proteins inside the mammary gland cells. All of the described biomarkers are involved in amino acid, carbohydrate, or lipid metabolism, suggesting that heat stress influences metabolic pathways in lactating dairy cows. More in-depth research is needed to elucidate the milk-related alterations in metabolic pathways in heat-stressed lactating dairy cows.

Moreover, Liu et al. (2017) conducted a simulated acute heat stress experiment (THI up to 84) to study the effects of heat stress on milk lipid composition. The authors detected marked changes in triacylglycerol (TAG) and polar lipid profiles between heat-stressed and non-heat-stressed cows. Heat stress caused decreased levels of TAG groups containing short- and medium-chain fatty acids and increased levels of TAG groups containing long-chain fatty acids. Furthermore, phosphatidylserine, phosphatidylethanolamine, lysophosphatidylcholine, phosphatidylcholine, and glucosylceramide levels were markedly lower during heat stress than under control conditions. These phospholipids could thus be used as heat stress biomarkers for dairy cattle. Notably, heat stress-induced alterations in TAG profiles can change the physical properties of milk fat, and reductions in phospholipids can influence the nutritional value of milk. Cowley et al. (2015) found that heat stress decreased the milk protein and casein concentrations but elevated urea concentrations. On the other hand, no influence of heat stress on lactose or milk fat concentrations were detected, indicating a specific reduction of mammary protein synthesis without any effects on total mammary activity. Furthermore, heat-stressed cows had increased blood concentrations of urea and calcium.

2.3. Meat biomarkers

Heat stress has been found to deactivate and enhance aggregation of the enzymes luciferase and β-galactosidase in mouse cells (Nguyen et al., 1989). In skeletal muscle cells, oxidative stress results in muscle degradation and myofibrillar disorganization (Koh and Escobedo, 2004). Moreover, oxidative stress causes biochemical alterations in cardiac muscle that result in muscle degeneration under ischaemic conditions (Fan et al., 2005). Hyperthermia in skeletal muscle cells activates transcription factors known as heat shock factors (HSFs), which are transferred to the cell nucleus and then phosphorylated. HSFs bind to heat shock elements (HSEs) of HSP genes, leading to the creation of the small HSPs HSP27 and αβ-crystallin (Paulsen et al., 2007). Cruzen et al. (2015) found that heat stress elevated or changed many proteins involved in glycogenesis, glycolysis, and glycogenolysis, suggesting that glycolytic capacity increases in response to heat stress. Moreover, heat stress reduced soluble actin and tubulin but elevated phosphorylated cofilin 2, suggesting a loss of microtubule structure and an increase in stable actin microfilaments. Furthermore, heat stress elevated manganese superoxide dismutase (SOD) but lowered peroxiredoxin 2, indicating an antioxidant response to heat stress. Therefore, the proteomic reaction to heat stress suggests significant alterations in cellular antioxidant machinery, structure, and carbohydrate metabolism and in skeletal muscle. Future mitigating solutions are needed to decrease the detrimental influences of acute heat stress on muscle function.

2.4. HSP family

HSPs are an intracellularly synthesized family of proteins that are extremely conserved and pervasive and are stimulated in response to several stress factors (Liu and Steinacker, 2001; Catalani et al., 2010; Abd El-Hack et al., 2018). Previous investigations have concluded that HSPs might be stimulated via physiological stresses (such as cell differentiation, caloric restriction, growth factors, hormonal stimulation, and tissue development), pathological stresses (such as parasitic or bacterial infections, inflammation, and fever), and environmental stresses (such as heat or cold stress, oxidative stress, UV radiation, amino acids, and heavy metals). Thermal stress can modify normal cellular responses, cause many anomalies in cell biological function, modulate metabolic reactions and cell membrane functions, induce oxidative cell damage, and activate both necrosis and apoptosis pathways that lead to cell death (Du et al., 2008; Slimen et al., 2016). HSPs, which are involved in protein synthesis, can be classified into several subgroups of molecular chaperones and categorized into 5 families according to their molecular weights (small HSPs, HSP60s, HSP70s, HSP90s and HSP100s) (Kristensen et al., 2004). At the level of cellular responses, HSPs are considered to be protective agents against stress factors; this protective role of HSPs is usually attributed to their chaperone function, which relies on their ability to join with denatured proteins and prevent their irreversible accumulation (Collier et al., 2008). The heat shock response is organized by four HSFs, HSF1, HSF2, HSF3, and HSF4, that link to HSEs in DNA (Fujimoto and Nakai, 2010), to initiate HSP expression. Archana et al. (2017) reported that large eukaryotes produce HSF1 to HSF4 and that HSF1 is directly connected to thermotolerance in livestock. Heat stress activates HSF1 and HSF3, whereas other stressors activate HSF2. HSF2 supports the continued expression of chaperones and acts as a regulator for misfolded protein degradation, and coordination of multiple HSFs protects cells from unfolded proteins. HSF1 is the main regulator of HSP70 gene expression (Archana et al., 2017). In the absence of heat stress, HSF1 is a monomer located in the cytoplasm; during heat stress, HSF1 dissociates from HSP and trimerizes with other HSF1 monomers before translocating to the nucleus. The HSF homotrimer binds to HSE in the nucleus and is hyperphosphorylated, leading to increased expression of HSP mRNA (Collier et al., 2008).

In bovines, Kristensen et al. (2004) reported that HSP72 (the inducible protein in the Hsp70 family) may be totally absent or maintained at minimal concentrations under normal environmental conditions. In addition, Chauhan et al. illustrated that HSF1 mRNA and HSP70 mRNA in skeletal muscles are increased by 1.3- and 3.5-fold, respectively, in response to heat stress. Under heat stress conditions (28–40 °C and 40–50% relative humidity for 2 weeks), HSF1 tends to be bound to DNA, subsequently enhancing transcription of HSP70 genes (coding for chaperone proteins) (Pirkkala et al., 2001; Chauhan et al., 2014c). This increased expression of HSP70 could play a key role in protecting cells against heat injury, which may thus be attributed to stimulation of the HSF1 signalling pathway. Similarly, Pearce et al. (2013a) reported increases in HSP70 mRNA expression in the muscle of pigs after exposure to continuous high ambient temperature (35 °C ± 1 °C). Additionally, sheep reared under high environmental temperature show increased expression of HSP70 in mononuclear blood cells, which can play a vital role in regulating body temperature (Romero et al., 2013). In the same context, greater expression of HSP70 in adipocytes has been reported in beef steers reared under heat stress conditions than in those reared in shaded locations (temperature range from 18 °C to 43 °C) (Di Giacomo et al., 2014). Generally, HSP70 expression is considered to be a valuable signal for alterations in body temperature (greater than 38.6 °C) (Gaughan et al., 2013). Thus, it under heat stress, elevated expression of HSP70 may be accompanied by enhanced thermotolerance due to vigorous cytoprotective consequences and enhanced protein refolding (Horowitz, 2001; Collier et al., 2008; Chauhan et al., 2014b, 2014c). Horowitz (2002) reported that HSP72 plays the main role in cellular defence against environmental heat stress, and increased expression of HSPs (HSP90 and/or HSP70) decreases respiration rate and rectal temperature and maintains feed consumption rate in sheep (Chauhan et al., 2014c). HSP90 is a critical and highly conserved member of the HSP family that is present in normal cells, plays a pivotal role in cellular adaptation to stress and regulates cell functions (Pratt, 1997). Chauhan et al. (2014c) observed substantial fluctuations in overall HSP90 expression in skeletal muscle of heat-stressed sheep (28–40 °C and 40–50% relative humidity for 1 week). Furthermore, Di Giacomo et al. (2014) concluded that HSP90 expression in adipocytes obtained from muscle tissue of beef cattle reared under mild chronic heat stress was higher than that in adipocytes from muscle tissue of animals raised under shade. The potential role of the HSP family under heat stress conditions is quite interesting; these proteins may have the ability to attenuate heat stress-induced oxidative damage and provide cytoprotection (Chauhan et al., 2014c). In another study, Deb et al. (2014) concluded that the Sahiwal (*Bos indicus*) breed of cattle have higher HSP90 expression than Frieswal (*Bos indicus* × *Bos taurus*) cattle, which adjusts their body temperature and enhances cell survival rates in high-temperature surroundings. The authors hypothesized that HSP90 expression kinetics differ between the two breeds due to differences in cell membrane properties. Elevated HSP90 levels are useful during stress conditions because HSP90 binds to glucocorticoid receptors and maintains their availability for cortisone binding (Grad and Picard, 2007). Moreover, Paula-Lopes et al. (2003) detected a less deleterious influence of heat shock on the number of cells per embryo and on blastocyst formation in the Brahman breed than in the Holstein and Angus breeds, indicating that the capacity for transcription in response to heat stress may be important and may be due to genetic variation between the European and Brahman breeds. Basiricò et al. (2011) observed that polymorphisms in the 5′ UTR accompanied elevated protein expression of HSP70 and elevated peripheral blood mononuclear cells (PBMC) viability, indicating a genetic mechanism of thermotolerance. Collier et al. (2006) detected elevated expression of Hsp90 in cultured bovine mammary epithelial cells obtained from Holstein Friesian cows after heat shock. Elevated Hsp90 expression during summer stress may result from rapid induction of Hsp90 protein translation to protect cells from heat stress. However, the functions of HSP family proteins need to be further explored to better understand their promising role in thermoregulation.

2.5. Inflammatory gene (NF-κB and tissue TNF-α) expression

Chauhan et al. (2014c) found that when crossed ewes (Merino × Poll Dorset) are exposed to high temperatures of 28–40 °C and relative humidity ranging between 40% and 50% for one week, they exhibit increases in both TNF-α mRNA expression in tissue (5.7-fold increase; $P = 0.013$) and NF-κB mRNA expression in skeletal muscle (5.2-fold increase; $P = 0.005$). Few studies have reported that the expression of select important genes (such as TNF-α, NF-κB, and JNK) involved in inflammation is promoted by oxidative injury related to heat stress (Chauhan et al., 2014c). In addition, it is well established that NF-κB is the main regulator of inflammatory signalling, through which it plays a vital role in the synthesis of proinflammatory cytokines. However, Montilla et al. (2014) revealed that even with increased ROS and TNF-α levels, pig skeletal muscle exposed to elevated environmental temperature for one or three days shows conflicting fluctuations related to oxidative injury and NF-κB signalling. Lambert (2004, 2009) and Pearce et al. (2013b, 2013c) reported that high ambient temperature resulted in increased expression of proinflammatory mediators (such as TNF-α); this effect may have been due to acute intestinal ischaemia with subsequent induction of leaky gut and compromise of intestinal barrier integrity, possibly leading to permeation of lipopolysaccharides into the blood circulatory system. Moreover, it has been reported that elevated expression of TNF-α, which is involved in promoting systemic inflammatory responses, is associated with heat stress and depression of feed consumption (Bradford, 2012; Chauhan et al., 2014c).

In heat-stressed sheep, Chauhan et al. (2014c) reported that skeletal muscle expression of TNF-α was augmented and accompanied by increased plasma levels of advanced oxidation protein products (AOPPs), resulting in excess oxidative stress. This upregulation of both AOPPs and TNF-α has attracted extraordinary attention, as these proteins are mediators of proinflammatory responses and biomarkers of protein oxidation. Celi (2011) specified that chronic heat stress leads to detrimental proinflammatory responses that may reduce animal productivity.

Notably, Montilla et al. (2014) reported elevated protein levels of TNF-α in the semitendinosus muscles (red muscle) of pigs exposed to one or three days of heat stress. Additionally, high environmental temperatures may activate pathways of cellular death by mediating survival pathways and stimulate JNK via activation of extracellular signal-regulated kinases and protein kinase B (Gabai and Sherman, 2002).

One explanation clarifying the changes in TNF-α expression is that heat stress from high environmental temperatures could mildly stimulate JNK expression, in turn stimulating apoptosis and HSP72 accumulation (Gabai et al., 2002; Gabai and Sherman, 2002; Montilla et al., 2014); subsequently, exposure to various stressors could inhibit JNK expression, thus downregulating the expression of inflammatory genes (TNF-α and NF-κB) and resulting in reduced respiration rate, rectal temperature and feed consumption in ruminants.

2.6. Oxidative stress markers

During the metabolic process in various cell organelles, several types of ROS are generated, such as hydrogen peroxide (H_2O_2), superoxide (O^{2-}), and peroxynitrite, that could be involved in crucial functions in numerous basic physiological pathways. However, excessive ROS production can disrupt antioxidant defence enzymes, producing oxidative stress in ruminants (Celi, 2011). As previously mentioned, complications of heat stress are increased under conditions of excessive ROS synthesis and diminished antioxidant defence, resulting in oxidative injury (Bernabucci et al., 2002; Di Trana et al., 2006; Chauhan et al., 2014b). Nevertheless, the specific pathways or mechanisms by which heat stress impacts the production of excessive ROS or reduces antioxidant potential remain elusive. In several poultry studies, it has been proposed that acute heat stress induces the generation of mitochondrial superoxide in skeletal muscle tissue, which results in oxidative impairment of lipid and protein synthesis in mitochondria (Mujahid et al., 2005). Mitochondrial respiration is known to be responsible for ROS generation, with complexes I and III presently observed as partial contributors (Rhoads et al., 2013a).

The skin is the main body organ contributing to heat loss and could be considered the largest organ; the skin acts as the main intermediate between the body and the surrounding environment and is continuously exposed to various physiochemical stressors in the environment (Athar, 2002; Maibam et al., 2018). An Indian research group (Maibam et al., 2018) evaluated oxidative stress markers (glutaredoxin (GRx), GPx and ROS) in skin cells of cattle with various coat colours in various seasonal conditions to examine and compare the adaptability of biochemical and physiological skin functions to high environmental temperatures between Zebu and Karan Fries heifers. At cold and hot ambient temperatures, the levels of ROS synthesis in both Zebu and Karan Fries cattle were significantly higher than those at moderate temperatures. However, ROS concentrations in skin tissue were significantly ($P < 0.05$) higher in Karan Fries cattle than in Zebu cattle during a hot environmental period (Maibam et al., 2018).

This climatic alteration in ROS levels in cattle skin might be due to the harmful impacts of heat stress on cellular responses in the skin. It has been reported that high environmental temperatures increase ROS production in HEK293 cells (Skibba et al., 1991; Kim et al., 2005; Maibam et al., 2018). In addition, mononuclear blood cells show abundant generation of ROS in cattle exposed to high environmental temperatures (Lacetera et al., 2006; Yang et al., 2010). At the mitochondrial level in animals, mitochondrial respiration and subsequent ROS generation are adversely affected by elevated temperatures (Heise et al., 2003). In response to elevated ROS levels, NRF2 expression and the expression of related antioxidant genes, such as PRDX1 and CAT, are greater in bovine granulosa cells subjected to elevated temperatures than in cells subjected to normal temperatures.

Notably, Alemu et al. (2018) studied the impact of exposure to a high environmental temperature (41 °C) versus a control temperature (37 °C) for 24 and 48 h on cultivated bovine granulosa cells. They found that stress marker genes of the endoplasmic reticulum (ER), namely, GRP78 and GRP94, were highly expressed after 24 h of heat stress, as were apoptotic genes, namely, Caspase-3 and Bax; in addition, they found aggregation of GRP78 protein and reduced regeneration of bovine granulosa cells. Altogether, these findings suggest that heat stress stimulates apoptosis and ROS synthesis and reduces cellular proliferation with subsequent activation of NRF2-induced oxidative injury and ER responses in bovine granulosa cells.

2.7. Antioxidants indices

2.7.1. GPx

High environmental temperatures have been found to be involved in stimulating oxidative stress through ROS generation or by diminishing the activity of antioxidant defence enzymes (Trout et al., 1998; Bernabucci et al., 2002; Chauhan et al., 2014b, 2014c). GPx enzymes (GPx1-GPx4) and thioredoxin reductase, which are critical defence enzymes, have important functions in cell protection against oxidative impairment (Hefnawy and Tortora-Perez, 2010; Chauhan et al., 2014b). Chauhan et al. (2014c) suggested that chronic heat stress tended to ($P = 0.070$) decrease GPx-1 mRNA in muscle tissue of sheep exposed to temperatures of 28–40 °C and relative humidity of 40–50% for one week. Recently, a study conducted by Guo et al. (2018) revealed that cows reared under heat stress had 63.25% lower plasma GSH-Px activity ($P < 0.05$) than the normal group. However, there were significantly higher ($P < 0.05$) levels of these enzymes in the skin in Zebu and Karan Fries cattle in the summer and winter seasons than in the spring, although at high environmental temperatures, the levels of GRx and GPx were significantly higher in Karan Fries cattle than in Zebu cattle.

The levels of GRx and GPx were found to be higher at an environmental temperature of 46 °C than at 28 °C in Marwari goats (Maan et al., 2013), cattle (Lakritz et al., 2002) and Holstein cows (Bernabucci et al., 2002); when these animals were exposed to stress conditions, the mean rectal temperature was 39.5 ± 02 °C and the mean daily THI was 73.2 ± 2.5. Similarly, Yun et al. (2012) found that cyclic heat stress (23–38–23 °C over 2 h on each of seven consecutive days) raises the concentration and mRNA expression of hepatic GPx in rats. Kumar (2005) also reported increases in the levels of blood GRx and GPx in buffaloes and cattle reared at 40 °C, suggesting that these increases act as compensatory mechanisms against the oxidative stress induced by heat stress (Daader et al., 2016; Abdelnour et al., 2012). In Karan Fries cattle, elevated concentrations of oxidative stress biomarkers during heat stress indicate excessive generation of ROS in skin tissue compared to that in the skin of Zebu cattle (Gihan et al., 2009). Similar to the study by Gihan et al. (2009), a recent study conducted by Maibam et al. (2018) revealed significantly altered physiological parameters and oxidative enzyme (GPx and GRx) levels in skin cells of Zebu cattle compared to Karan Fries cattle during the summer season and suggested that these alterations might be due to differences in heat tolerance between the breeds. Finally, Rathwa et al. (2017) found that plasma GPx levels in Indian indigenous sheep were 1.29-fold higher ($P < 0.05$) during the hot season than in the mild season (the THI values for summer and winter were 82.55 and 59.36, respectively).

2.7.2. SOD

Mitochondrial SOD is one of the most important cellular defence enzymes; it can enhance the production of superoxide free radicals in the mitochondrial electron transport chain and prevent oxidative damage to the mitochondrial membranes (Mates et al., 1999). Chauhan et al. (2014c) reported that the mRNA expression of muscle SOD-2 was reduced by 60% in sheep exposed to chronic high temperatures ($P = 0.015$). It appears that continuing heat stress downregulates antioxidant enzymes with subsequent elevations in oxidative stress. While augmented expression of SOD and catalase (an antioxidant enzyme) was found in the semitendinosus red muscle of pigs after 24 h of high ambient temperature, the expression returned to normal levels after three days of high ambient temperature (Montilla et al., 2014). Additionally, Rathwa et al. (2017) found that plasma SOD in Indian indigenous sheep was higher (1.46-fold higher, $P < 0.05$) during the summer season than during the winter season.

The observed impacts of heat stress on the expression of antioxidant enzymes (SOD-2) are surprising, as we would have predicted that increased antioxidant enzyme activity resulting from augmented expression would reverse the oxidative stress caused by heat stress.

2.7.3. MDA

MDA is a sensitive biomarker of oxidative stress; therefore, the elevated MDA levels documented in heat-stressed animals strongly indicate that the period of heat was indeed stressful to these animals and had negative impacts on immune responses. According to the findings of Guo et al. (2018), heat-stressed cows have greater plasma MDA concentrations (133.4% greater) than cows reared during the autumn season, suggesting that heat stress can impair immune defence by depleting antioxidant enzymes. High environmental temperatures inhibit the activity of antioxidant enzymes and increase lipid peroxidation in intracellular pathways (Liu et al., 2014; Guo et al., 2018). Zuo et al. (2000) also conveyed that heat stress can stimulate extracellular and intracellular superoxide generation; ROS synthetized by superoxide can attack membrane lipid composition and therefore initiate lipid peroxidation (Halliwell and Chirico, 1993). The activity of antioxidant enzymes is inhibited by enhanced accumulation of MDA in the mitochondria of cells (Mujahid et al., 2007). However, Indian indigenous sheep do show increased levels of plasma LPO (1.31-fold greater, $P < 0.05$) in periods of high temperatures (THI value =82.55) than in winter (THI value =59.36) (Rathwa et al., 2017).

2.8. Skin colour genes (PMEL and MC1R)

Adaptation is the ability of an animal to regulate physiology or behaviour in response to adverse environmental conditions or to make genetic adjustments that allow it to resist various environmental stresses (Maibam et al., 2014). It has been reported that biochemical, morphological and physiological responses to heat stress differ according to the genetic makeup of the animal as well as the environmental conditions. Seasonal variations and environmental conditions are major factors that influence livestock traits. As mentioned previously, the skin has a potential role in reducing heat loads in mammals. The amount of melanin pigment present (either pheomelanin or eumelanin) determines the coat colour of an animal; the pheomelanin pigment is responsible for reddish brown, reddish tan, and yellow colours, while eumelanin is responsible for black and brown colours (Simon and Peles, 2010). Regulation of pigmentation in cattle skin affects various important factors, including the function of the skin in photoprotection against UV damage, social and cosmetic factors and different pigmentary diseases. Many genes are engaged in regulating mammalian pigmentation and are expressed during the creation, differentiation, survival and/or environmental responses of melanocytes (Maibam et al., 2014, 2018). McRobie et al. (2014) reported that the MC1R gene plays a role in pigmentation variances in mammals. Moreover, one MC1R allele encourages black pigment, which protects skin against UV injury (Greave, 2014). Moreover, PMEL is a melanocyte protein that plays a role in the deposition of eumelanin (McGlinchey et al., 2009). Hence, the PMEL and MC1R genes can direct the pathway of melanin production towards pheomelanin rather than eumelanin (true melanin). Coat structures are also linked to animal performance and heat tolerance (Collier and Collier, 2012). In animals, skin pigmentation and hair characteristics are extremely visible features; thus, coat colour is related to the general state of health of the animal (Stephen et al., 2011).

The gene expression of PMEL and MC1R is upregulated during cold and heat stress; however, high environmental temperatures apparently have a greater effect than cold stress (Maibam et al., 2018). Additionally, Maibam et al. found that the expression of skin colour genes, which are involved in skin protection, is higher in winter than in summer. This reveals that the protective capability of skin against heat stress is less than that of skin against cold stress in Karan Fries and Zebu cattle (Maibam et al., 2018). The different expression features of such genes in skin cells during different seasons could be a key reason why the animals absorbed less heat in hot weather while absorbing more heat in cold weather. It is well known that mammals utilize numerous mechanisms, including physiological, behavioural and genetic thermoregulatory responses, to alleviate heat loads.

Animals exposed to hot ambient temperatures search for shade or adjust their orientation to avoid the sun. However, animals exposed to low ambient temperatures try to orient their bodies for exposure to sunlight (Blackshaw and Blackshaw, 1994). During cold weather, animals expose themselves to sunlight to sustain their body temperatures. However, this might also increase production of melanin and further increase absorption of heat during cold conditions, since the exposure to sunlight might play an essential role in pigmentation of the skin (Barnicot, 1977). Increased expression of colour genes (PMEL and MC1R) in the skin of Zebu cattle might increase synthesis of eumelanin in skin cells to levels greater than those in the skin of Karan Fries cattle. The MC1R gene has a high binding capacity for ACTH and α-MSH (Mountjoy, 1994), which stimulate eumelanin synthesis and lead to skin darkening (Suzuki et al., 1996).

The increased synthesis of eumelanin pigment could induce inhibition of ROS synthesis and oxidative injury during heat stress in Zebu cattle as compared to Karan Fries cattle (Maibam et al., 2018). Eumelanin is counted as a grubber of ROS production in the skin cells (Meredith and Sarna, 2006), its effectiveness in scavenging reactive oxygen species and blocking ultraviolet rays (UV) will support its role in photoprotection (Klungland et al., 1995).

Likewise, melanin has powerful antioxidant ability in skin tissues (Song et al., 2009). Therefore, a minor amount of pigment in skin tissues able to induce greater oxidative injury than dark pigmented coat under a hot climatic condition in cattle. This phenomenon could discuss the dark skin pigmentation, which has excellent tolerant to heat than a minor pigmented coat.

So far, animals live in a hot climatic condition (such as Zebu cattle) have increased expression of colour genes in skin cells; so, it usually showed dark pigmentation as compared to animals in cold areas, with a subsequent increase in skin protective capability and decreasing in oxidative injury under environmental heat stress. Collectively, expression of colour genes may discuss the superiority of zebu cattle breed in heat tolerance.

2.9. Interleukin

Interleukins are a collection of cytokines that were first detected in leukocytes (Brocker et al., 2010). Most interleukins are synthesized by monocytes, helper CD4 T lymphocytes, endothelial cells, and macrophages. They enhance the differentiation and development of B and T lymphocytes and hematopoietic cells. The higher relative mRNA expression of IL-6 and IL-2 was detected in winter than summer in tropical and temperate region goats (Marai et al., 2001), which reported that the HPA axis is stimulated under stress conditions, which stimulate the secretion of glucocorticoids and catecholamine, which modulate immune cells. Therefore, a higher expression of proinflammatory cytokines like IL-2 and IL-6 modulate cold stress. Lefcourt and Adams (1998) detected that acute heat stress significantly promoted the splenic lymphocytes to secrete IL-2 in broiler chickens. The lowered IL-6 expression during summer may be because of the suppression of IL-6 expression mediated by stimulating transcription factor 3 by heat shock factor 1 as detected in murine cells (Crawshaw, 1980). A well-developed thermoregulatory protective mechanism detected in adults versus to infants and aged ones (Nikitchenko et al., 1988). The higher expression of IL-6 and IL-2 in adults more than young ones, indicating more heat protection in adults as compared to young ones.

Sheikh et al. (2017) reported that when Karan Fries cows exposed to heat stress, they showed significant increase ($P < 0.05$) in their blood content of IL-6 (1.32 times), and significant decrease in IL-12 concentration as compared to control group (51.58 ± 6.03 v/s 62.05 ± 9.11 pg/ml). Records from human studies revealed that IL-6 gets raised during high environmental temperature (Hammami et al., 1997). Likewise, it was recognized that heat stress magnifies TNF and IL-6 levels in males (Starkie et al., 2005). Moreover, IL-12 levels had diminished during heat stress as much the elevation of IL-10 concentration, which is a strong inhibitor for IL-12 (Sheikh et al., 2016).

Heat stress can affect immune response by heat shock proteins like HSP70 which contribute to immunity activation by linking Toll-Like Receptors (TLRs) (Takeda and Akira, 2003). TLRs are mainly expressed on the antigen presenting cells like macrophages, monocytes, B lymphocytes and dendritic cells (Yan et al., 2007). The expression pattern of TLR mRNAs have been detected in buffalo (Vahanan et al., 2008), goat (Tirumurugaan et al., 2010) and cattle and sheep (Menzies and Ingham, 2006). TLRs has a pivotal role in innate immune induction during heat stress in goats (Paul et al., 2015). During heat stress, Toll-like receptor 4 (TLR4) and Toll-like receptor 2 (TLR2) identify the damage-associated molecular patterns to produce many pro-inflammatory cytokines triggering the host immune response (Kawai and Akira, 2010). Moreover, heat stress modifies the expression dynamics of pro-inflammatory cytokines like PBMCs and IL6 mRNA expression in livestock (Ju et al., 2014), IL2 mRNA expression in goat (Maurya et al., 2013).

Heat shock causes a quick increase in the level of TLR4 and TLR2 expressions in human monocytes, indicating the heat shock effect on the overall responses of immune cells to pathogen-associated molecular patterns (PBMCs). Moreover, it was detected that HSP might stimulate the TLR4 and TLR2 (Matzinger, 2002). It is reported the HSP70 induction by heat shock in buffalo PBMCs (Mishra et al., 2011), bovine PBMCs (Lacetera et al., 2006) and bovine lymphocytes (Guerriero and Raynes, 1990). Therefore, a powerful link may exist between TLR and HSP expression by heat stress. Heat shock stress might influence TLRs expression in immune cells to stimulate all adaptive and innate immune systems to combat against pathogenic microorganisms (Chen et al., 2005). Recombinant HSP60, HSP70 can activate dendritic cells and monocytes to liberate cytokines and elevate their antigen presenting capacity by binding to TLR2, TLR4 (Gobert et al., 2004). In muscle, HSF could be identified as an element of IL6 transcriptional regulation (Welc et al., 2013). Hyperthermia-induced IL6 mRNA upregulation is mitigated by suppression of HSF1. The stimulation of the JAK-STAT pathway is included in TLR4-induced IL6 expression (Kimura et al., 2005). Asea et al. (2002) reported that TLR4 and TLR2 receptors with their cofactor CD36 and CD14 can initiate secretion of cytokine in an HSP70 dependent manner.

Hormones (Prolactin (Stocco et al., 2001), Thyroxine (Sivakumar et al., 2010), Leptin (Figueiredo et al., 2007), Glucocorticoids (Bharati et al., 2017), Growth hormone (Deane and Woo, 2005), Prostaglandin A (Collier et al., 2007), Estrogen (Zhang et al., 2004), Insulin (Li et al., 2006), and Melatonin (Sharma et al., 2013) are involved in the resistance against heat stress and could be pivotal markers for stress assessment in animals. Melatonin was reported to increased HSP gene expression (Sharma et al., 2013) and increase HSP gene expression in pancreatic AR42J cells (Bonior et al., 2005). Stocco et al. (2001) observed that prolactin stimulated HSP 60 in rodent luteal cells. Moreover, Leptin down-regulated HSP 70 in chicken liver and hypothalamus (Figueiredo et al., 2007). Furthermore, Prostaglandin A increased expression of HSP in bovine mammary epithelial cells (Collier et al., 2007). In addition, in cardiac tissue Insulin-stimulated HSP gene (Li et al., 2006). In the whole blood of sea bream, Growth hormone stimulated HSP in whole blood of sea bream (Deane and Woo, 2005). Zhang et al. (2004) detected that Estrogen and androgens increased HSP gene expression. In goats, Sivakumar et al. (2010) observed a reduction of thyroxine levels in plasma under heat stress. Reduced thyroid hormone level throughout heat stress is an adaptive response and influences the hypothalamic- pituitary adrenal to lower thyrotropin-releasing hormone, which decreases metabolic rate, and lowers the heat levels produced by the cells (West, 1999). Bharati et al. (2017) detected the elevation of serum cortisol concentration during short-term heat stress acclimation (STHSA) and gradually lowered during Long-Term Heat Stress Acclimation (LTHSA). Moreover, TLR 2 expression was up-regulated during STHSA and reduced to basal level during LTHSA. On the other hand, TLR 4 expression was up-regulated during STHSA and LTHSA. Furthermore, IL2 and IL 6 were up-regulated during STHSA and declined to basal level during LTHSA. In addition, the authors observed that IL 2/6 and TLR 2/4 has a pivotal role in thermotolerance in Tharparkar cattle during STHSA and LTHSA. The elevation in cortisol concentration can be considered as a marker of stress, which might enhance gluconeogenesis process to serve glucose throughout acute heat exposure period while the decrease in cortisol concentration might assist to lower the metabolic heat production in animals throughout chronic heat exposure period.

Strong et al. (2015) investigated the influence of heat stress during late gestation on calf immunity. Calves were born to cows exposed to evaporative cooling (CT) or HS (cyclic 23–35 °C) for 1 wk at 3 wk before calving. The HS calves had low levels of TLR2 and tumor necrosis factor-α (TNF-α) and higher levels of TLR4, IL-1 receptor antagonist (IL-1RA), and IL-1β in the first week after calving compared with CT calves then decreased after day 7. Moreover, the HS calves had a higher percentage of CD18 + cells than CT calves. Furthermore, a lower number of lymphocytes and a higher number of neutrophils were in the HS calves compared with the CT calves. The authors suggested that the lower TNF-α concentration could be attributed to an elevation of circulating stress hormones in the intra-uterine calves. Interleukin-1RA acts as a competitor with the Interleukin-1 (IL-1) receptors, so suppress IL-1. Moreover, heat stress upregulated the levels of IL-1RA and IL-1β in rats (Lin et al., 1995) and calves (Strong et al., 2015). Furthermore, some investigations detected the protection of IL-1RA against heat shock damage in rats (Lin et al., 1995) and rabbits (Lin et al., 1994). Therefore, the higher IL-1RA level in the first week after calving was essential to counter the IL-1β elevation during the prenatal HS. Furthermore, TLR4, IL-1β, and IL-1RA reduced after day 7, indicating the heat stress end on the calves. So, the maternal heat stress influences the biomarkers of embryos' immunity during late gestation and recovered after the heat stress end after parturition.

2.10. Liver proteomics

Metabolic alteration of the liver is perilous for successful adjustment of the physiological and biochemical pathways to any adverse environmental stressors. It is well documented that the liver is a central organ coordinating in lipid, carbohydrate, and protein metabolism. Heat stress induces several homothetic mechanisms that prioritize thermoregulation over other physiological processes (Baumgard and Rhoads, 2013). As a result, heat-stressed cows have markedly reduced milk production throughout lactation and are more susceptible to metabolic disorders during the transition period (Kadzerea et al., 2002;

Bernabucci et al., 2010; Tao and Dahl, 2013).

Limited evidence from targeted gene studies indicates that heat stress during the dry period alters mammary gland remodeling and hepatic lipid metabolism (do Amaral et al., 2009, 2011; Tao et al., 2011). Recently, Skibiel et al. (2018) reported an alteration in proteomics analysis and protein abundance in the liver of transitioning cows exposed to a hot climate or cold environment conditions during the dry period. Heat-stressed cattle have impaired mitochondrial function and altered lipid, carbohydrate, and amino acid metabolism in the liver, as indicated by the top canonical pathways and biological functions identified by IPA. Based on the differential abundance of proteins in these pathways, it seems probable that heat-stressed cows have reduced ATP synthesis, greater oxidative stress, shifts in the precursor supply for gluconeogenesis, and accumulation of the hepatic lipids in the liver that may contribute to fatty liver disease. Thus, these changes in liver function may be associated with transition-related diseases and poor lactation performance. Overall, our results indicate that cooling dry cows improves liver function during early lactation, and thus provides greater metabolic support for higher milk yields compared with cows that are heat stressed when dry.

2.11. Heat-stress mitigation

Suitable mitigation strategies against mischievous influences of heat stress on livestock must be achieved to keep high productivity during times of heat stress. Mitigation strategies differ according to the species, resources (natural and economic) and region. The management plans could be cooling technologies, nutritional additives, and genetic improvements. Moreover, alleviating the adverse influences of hyperthermia can provide appropriate animal welfare standards.

3. Environmental strategies

Heat-stress management strategies differ according to resources, region, and species. In dairy cattle species, decreasing heat stress by sprinkler systems with air-circulating fans is effective (Turner et al., 1992), particularly in low humidity climates (Morrison et al., 1973). Moreover, averting transport, restraint, and vaccinations throughout the hottest times, and supplying shades can save livestock from heat stress. Shading systems protect livestock from direct solar radiation is an economical heat stress management strategy in most countries and can minimize the adverse influences of heat stress on the livestock body temperature (Fournel et al., 2017). Furthermore, the utilizing of cooling pads may lower the heat stress influences on lactating-sow thermoregulation and productivity (Cabezón et al., 2017). Lastly, building design has a pivotal effect on livestock health throughout heat stress. In pigs, building engineering must take into consideration changing heat climates and animal heat production (Brown-Brandl et al., 2003) to confirm the balance between heat accumulation and building heat removal. In addition, closely monitoring cooling systems to avert rapid temperature variations can promote sow's reproductive capacity. Quick cooling after acute heat stress leads to a pathological condition characterized by skin vasoconstriction, resulting in a whole-body inflammatory response (J. Johnson et al., 2016; J.S. Johnson et al., 2016). Sows suffered from quick cooling before breeding has lowered viable-fetus count, possibly because of higher circulating tumor necrosis factor (TNFα) and elevated insulin resistance (J. Johnson et al., 2016; J.S. Johnson et al., 2016). So, higher insulin resistance can lower oocyte quality (J. Johnson et al., 2016; J.S. Johnson et al., 2016b) because insulin is an essential component in normal oocyte function and development (Ou et al., 2012).

4. Nutritional strategies

Nutritional strategies can complement environmental management throughout prolonged heat stress. In pigs, formulating energy-dense low-fiber diets as fiber can elevate the heat increment of feeding (Curtis, 1983), so may reduce the heat production. On the other hand, keeping enough fiber amount is needed for keeping rumination in ruminant species (West, 1999). Elevating energy density to lower the heat rise of diets can help in maintaining body temperature throughout heat stress, but this should be equated with the suitable implication of fiber in ruminant diets to keep productivity and health. Moreover, appropriate insulin action is required for surviving and adopting a heat load. So, researchers enhanced insulin sensitivity by the supplementation of insulin-sensitizing additives like chromium (Mertz, 1993), thiazolidinediones (Ranganathan et al., 2006) or lipoic acid (Diesel et al., 2007) can ameliorate animal performance throughout heat stress (Rhoads et al., 2013b).

In addition to changing metabolic heat production and post-absorptive metabolism, targeting specific tissues with nutritional additives may enhance heat stress bearing and recovery. The gastrointestinal (GI) tract is oversensitive to the heat stress influences and is a purpose that could be achieved through nutritional interventions. Heat-stressed animals switch blood flow to the periphery to elevate heat loss, resulting in GI tract damage due to hypoxia (J. Johnson et al., 2016; J.S. Johnson et al., 2016). To relieve this damage, nutritional strategies can be performed like the implication of betaine (Hassan et al., 2011), zinc (Zhang and Guo, 2009) or L-glutamine (Johnson and Lay, 2017). L-glutamine is an essential amino acid that is the main energy source for quickly dividing cells such as lymphocytes and enterocytes (Reeds and Burrin, 2000), so it is considered as an immunomodulator that suppresses pro-inflammatory cytokines (Jiang et al., 2009a, 2009b). L-glutamine addition enhances intestinal barrier function by improved prohibiting of intestinal atrophy, oxidative-defense capacity, higher nutrient absorption and enhanced antibacterial activity (Jiang et al., 2009a, 2009b). Moreover, L-glutamine enhances milk production in dairy cattle under heat stress (Caroprese et al., 2013) and elevates productivity of newly weaned pigs during heat stress periods (Johnson and Lay, 2017). In acute and chronically heat-stressed pigs, the addition of Zinc may enhance intestinal integrity because Zinc is pivotal for the healthy intestinal barrier (Fernandez et al., 2014). Zinc mode of action may be upregulation of tight junction proteins (Zhang and Guo, 2009), or an antioxidant function through metallothioneins induction (X. Wang et al., 2013; Y. Wang et al., 2013). Betaine is a methyl donor and osmotic regulator, which can prevent intestinal osmotic stress by lowering sodium-potassium pump activity (Cronje, 2005). Moreover, betaine improves the influences of heat stress on body temperature indices, immunity and weight gain in rabbits (Hassan et al., 2011), enhances milk-production parameters in dairy cattle.

5. Genetic selection

Developments in nutritional strategies and environmental modifications do not totally mitigate the heat stress influence on animal production throughout the Summer. Therefore, long-term strategies must be considered for more acclimation to heat stress periods. Variations in heat stress tolerance found among livestock species suggest genetic tools to select the high thermotolerant animals. The selection of heat-tolerant animals from high-producing breeds helps these animals to keep high productivity under heat stress periods. Cattle with lighter coat colour, shorter hair, and greater hair diameter are more acclimatized to heat stress than animals have darker colours and longer hair coats (Bernabucci et al., 2010). *B. Taurus* tropical cattle (Senepol and Carona) are characterized by this phenotype, and this dominant gene is accompanied with an elevated sweating rate in homozygous cattle during heat stress periods (Mariasegaram et al., 2007). Heat shock gene associated with thermotolerance was utilized as a marker in the genome-wide selection to choose thermotolerant bull that is used in the breeding program. Under heat stress, Hsp gene expression makes some alterations such as stimulation of HSF1, elevated Hsp genes expression and reduced expression of other proteins, elevated levels of amino acid and glucose oxidation and decreased fatty acid metabolism, endocrine system stimulation of the stress response and immune system stimulation through Hsp secretion outside the cells. By stress continuation, these gene expression shifts result in changed physiological state nominated as "acclimation"(Collier et al., 2008). May researchers detected the accompanying of SNP in the Hsp genes with tolerance in farm animals. Moreover, accompanying of polymorphisms in Hsp90AB1 with heat tolerance has also been observed in Sahiwal and Frieswal cattle (Deb et al., 2014), Thai native cattle (Charoensook et al., 2012), HSP70A1A gene (Q. Li et al., 2011), HSF1 gene (Q.L. Li et al., 2011), HSBP1 (Y. Wang et al., 2013) in Chinese Holstein cattle. Furthermore, there are non-Hsps genes detected to undergo expression alterations in response to heat stress, such as ATP1A1 gene in jersey crossbred cows (Das et al., 2015) and ATP1B2 gene in Chinese Holstein cows (Wang et al., 2011) which were detected to be accompanied with thermotolerance. These SNPs could be utilized as markers to develop thermotolerant animal in early ages. Furthermore, a thermotolerant bull can be utilized in breeding policy to have heat adapted offspring.

6. Conclusion

Data surveyed in the present review highlight the deleterious effects of heat injury on stress biomarkers, general health status and protein alteration of ruminants, and elucidate that heat injury able to induce adverse immune responses and several unfavorable impacts on oxidative status, heat shocks proteins, inflammatory response (NF-κB and TNF-α), skin colour genes (PMEL and MC1R) and fluctuations of proteomics profile in ruminants tissues etc. These influences are paying attention to the effect of adverse environmental condition on general health status and growth performance of livestock animals and encourage researcher to investigate those impacts. However, further investigations still required to understand the basic heat stress-induced mechanisms related to its deleterious effects on ruminants at the levels of gene or proteomics.

Conflict of interest

The authors declare that they have no conflict of interest.

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