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Review Article

Cattle be in Two Mind States: An Overview of Heat Stress Tolerance in Cattle

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Abstract

The heat stress stimulated by the environment is of vital interest as it negatively influences animal productivity. Therefore, adapting to challenging climate conditions is essential for agriculture because we can gain increased and environmentally friendly production by reducing stress on cattle. Heat shock proteins reveal the functions in the cells and handle their protection under stress situations. Therefore, it is essential to highlight the response mechanisms and genetics by which heat-stressed cattle survive under hot climate conditions. The current review provides insight into different genes, their functions and gene expression studies conducted in cattle under heat stress conditions. Genetics and genomics play roles in livestock health, as they will help the researchers understand the importance of heat shock proteins in livestock, especially in dairy cattle. © 2023 Friends Science Publishers

Keywords: Environment; Heat shock proteins; Gene expression; Adaptation; Heat stress response

Introduction

The necessities of people's life predominantly depend on livestock such as cattle, buffalo, goats and sheep. We use them for meat, dairy, leather, hair and other valuable products. However, differences in temperature, precipitation, or greenhouse gases in the atmosphere decrease animal production, reproduction and well-being (Thornton and Pierre 2010). Therefore, livestock must adapt to challenging climate conditions (Berman 2011). In tropical, subtropical, and dry regions, high atmospheric conditions are the primary reason for heat stress (HS) and the risk of decreased animal production (Belhadj *et al*. 2016). Heat stress is an environmental situation that causes the productive temperature to exceed the optimum temperature of the animal's thermal neutral zone (Hahn 1999). Therefore, the animal must regulate metabolic rate, acclimation and fat layer to combat HS conditions and control body temperature (Sejian *et al*. 2018). Moreover, animals undergo increased dietary requirements and genetic competence enhancement to meet the energy conversational process.

Noticeable environmental conditions have adversely affected cattle's health overall, especially in Pakistani cattle (Chaudhry Qamar Uz Zaman 2017). Clean Green Pakistan (CGP) is a flagship five-year campaign aiming to improve the ecological conditions, hence improving the climate scenario of the country. This program is essential to improve the stress conditions on cattle since Pakistan is ranked in the 8th position as per the "Global Climate Risk Index 2021" report by Germanwatch. According to a recent ranking, Pakistan has dropped from 5th to 8th, but livestock is still vulnerable to climate change (Eckstein *et al.* 2021). HS, cold stress, water availability, feed availability, water quality and disease spread severely affect the livestock. Every organism has a built-in system to change its physiological system to combat environmental changes, including cattle. One medium is to combat the HS by producing more Heat shock proteins (HSPs) (Wang *et al.* 2017). HS causes protein misfolding in cells and HSPs, as molecular chaperones, supervise the correct protein folding to maintain intracellular homeostasis (Arrigo *et al*. 2005). Initially, HSPs were found in the salivary gland cells of Drosophila due to heat shock treatment (Ritossa 1962), but later they were found in almost all organisms. However, they are expressed whenever cells are exposed to a high temperature above their optimum temperature. Moreover, these proteins may also produce when an organism's cells are exposed to toxicity or any other imbalanced state, lethal to cells, so these specific proteins are called stress proteins (DeRocher *et al*. 1991). There are different HSPs, including HSP40, HSP60, HSP70, HSP 90, etc. Each protein plays a significant role during HS acclimation. For example, HSP70 plays a vital role when the

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animal is under climate stress conditions, and it has been studied that HSP70 is an ideal molecular marker that secures the cells to counter heat shock exposure in varied livestock.

The current review highlighted the importance of HS tolerance in cattle. Many research discoveries show that Zebu cattle have high thermotolerance by regulating several changes in the body, metabolic rates and gene expression. Therefore, analyzing cattle's cellular responses to temperature stress, heat shock response components and stress on animal’s bodies is essential for improving local breeds for better production with many beneficial adaptabilities.

The impact of climate change on cattle

Climate change is now considered a global issue, and according to the WMO's report, there will be an increase of 3^0C to 5^0C in the current century (Barriopedro *et al.* 2020). First, the HS caused by climate change highly influences dairy cattle reproduction, growth, feed intake, and disease risk (Rojas-Downing *et al.* 2017). Second, the agriculture sector suffers considerable economic loss worldwide (Thornton *et al*. 2007). Consequently, to avoid these problems, several countries are developing crossbreeding programs for cattle to withstand HS and increase the quality of meat and milk production (Hoffmann and Beate 2006). For example, Pakistan has a variety of cattle, and some possess HS tolerance ability (Table 1).

The breeds of heat-tolerant cattle can better survive in harsh climatic conditions than non-tolerant ones. Some cattle undergo morphological changes in their body to adapt to heat or cold conditions (Das *et al*. 2016). Along with morphological changes in the body, cattle also undergo changes in its physiological, behavioral, biochemical, molecular, and endocrine mechanisms (Fig. 1). Usually, when an animal undergoes thermal stress, its behavior is observed to change at first instinct. Later in the stress period, physiological and other adaptation is observed in cattle. However, the cattle that exhibit heat tolerance have low growth rates, milk production, meat production, and reproductive efficacy. Thus, some effects of climate change are visible, but some damage the animal's body internally (Fig. 2).

Essential genes related to heat stress in cattle

HSPs are a group of proteins that play a crucial role in response to environmental stress on the host (Ghosh *et al*. 2018). Most family members of HSP work as chaperones and initiate during stress conditions to reshape the damaged cell proteins. Thus, the expression of HSPs is initiated with the induction of heat shock factors (Fig. 3). The heat stress response triggers the inactive HSP-HSF complex; this initiates the heat shock factors (HSF) synthesis and converts it into an active form. Protein kinases form trimmed HSF and transport it into the nucleus, where the trimmed HSF activates the heat shock elements (HSE) and starts the HSP transcription, producing HSP proteins. The final proteins are transported to the cytosol to perform different functions, such as combining with stressed-denatured protein and forming a refolded protein. Similarly, the translated HSP proteins can perform other functions under stress conditions.

The HSP family comprises many members (Table 2) and is found in almost all living organisms, including cattle. The molecular weight in kilos Dalton is present next to HSP's name (Moseley 1998). The animal's genetic makeup plays a huge role in the development of thermo-tolerant cattle, and scientists are focused on HSP markers and important miRNA to prevent heat-induced stress and ensure thermo-tolerant cattle breeds such as the Nekore breed (Hansen 2004). Some of the important studies conducted on HSPs with respect to HS in cattle are discussed below:

Heat shock protein 10

Heat shock protein 10 (HSP10) is also known as chaperonin 10 (cpn10) and the HSPE1 gene administrates its expression. The HSP10 act as a cofactor of HSP60 and is usually expressed during an immune response (Böttinger *et al*. 2015). Moreover, this protein is also related to other vital body functions, such as cancer, pregnancy and autoimmune inhibition.

HSP10 has also been found to be abundantly expressed during summer and winter in cattle (Sahiwal and Tharparkar) and Buffalo (Murrah) compared to spring (Kumar *et al.* 2015). The study used PBMCs to evaluate the expression using quantitative real-time PCR. Gene expression of HSPA1A and HSPA1B were significantly higher, followed by HSP10 and HSP60. Furthermore, the expression pattern of HSP10 was noticed to be higher in buffalo than cattle, implying that buffalo can withstand harsh environmental conditions and are better adaptive to climate stress.

Heat shock protein 27

Another essential heat shock protein is HSP27 (heat shock protein beta-1) and the HSPB1 gene encodes it. The HSP27 is also associated with numerous functions, including protein-controlling mechanisms, apoptosis inhibition, thermoregulation, cell development mechanism, signal transduction and cell differentiation (Nahleh *et al*. 2012).

Although most of the expression analysis of HSP27 is done in skeletal muscles, few studies have been conducted to check the HSP as a biomarker in serum under heat stress conditions (Min *et al*. 2015). Therefore, the Enzyme-linked immunosorbent assay (ELISA) was used to test HSP27, HSP70 and HSP90 in serum and other parameters: insulin, leptin, adiponectin, AMPK and HSF. After three weeks of stress, the samples were selected and daily milk yield, dry matter intake, rectal temperature, and respiratory rates were recorded. The average temperature-humidity index (THI) was set to 81.7 to meet the heat stress conditions.

Table 1: Cattle breeds across Pakistan and their details (Khan *et al*. 2008)

Names	Synonym	Heat tolerance	Utility	Distribution	Population Size	Other Countries
Achai	N/A	Yes	Light draught and dairy	KPK	684	Afghanistan
Bhagnari	Nari	Yes	Heavy draught	Baluchistan	1027	Endemic
Cholistani	N/A	Yes	Dairy	Punjab	537	Endemic
Dajal	N/A	No	Medium draught	Punjab	72	Endemic
Desi	N/A	No	Dairy and draught	All provinces	11752	India
Dhanni	Pothwari	No	Medium draught	Punjab	1483	Endemic
Gabrali	N/A	No	Light draught and dairy	KPK	231	Afghanistan
Hariana	N/A	No	Draught	Punjab	Less than 1	India
Hissar	N/A	No	Draught	Punjab	Less than 1	India
Kankrai	N/A	No	Medium draught	Punjab and Sindh	273	India
Lohani	N/A	No	Light draught	KPK and Punjab	560	Endemic
Red Sindhi	Sindhi/Malir	Yes	Dairy	Sindh and Baluchistan	3032	Endemic
Rojhan	N/A	No	Light draught	Punjab	376	Endemic
Sahiwal	Montgomery/Lola	Yes	Dairy	Punjab	2753	India, Kenya, Australia, and others
Thari	Tharparker/ Grey Sindhi	Yes	Medium draught and dairy	Sindh	1783	India

Table 2: List of important heat stress genes in cattle

Genes	Location	Function	Reference
ANTXR2	Plasma membrane	Transmembrane signaling receptor activity	(Flori *et al*. 2019)
BCL2	Cytoplasm	Ubiquitous inhibitor of cell death	(Corazzin *et al*. 2020)
BHLHE41	Nucleus	Controls the circadian rhythm and cell differentiation	(Jiang *et al*. 2019; Uchimura *et al*. 2019)
CDKN1B	Cytoplasm	Regulator of cell cycle progression	(Sigdel *et al*. 2019)
E2F8	Nucleus	Regulation of genes is required for progression through the cell cycle	(Jiang *et al*. 2019; Uchimura *et al*. 2019)
FBXO44	Cytosol	Functions in phosphorylation-dependent ubiquitination	(Jiang *et al*. 2019; Uchimura *et al*. 2019)
GATAD2B	Nucleoplasm	Represses gene expression by deacetylating methylated nucleosomes	(Jiang *et al*. 2019)
GLUT-1	Plasma membrane	Responsible for constitutive or basal glucose uptake	(Baumgard and Jr Robert 2013)
HSF1	Nucleus and Cytoplasm	Acts as a binder to HSEs and activates HSP gene transcription	(Khan *et al*. 2020; Collier *et al*. 2008; Rong *et al*. 2019; Kumar *et al*. 2015; Min *et al*. 2015)
HSP 10	Mitochondria	Chaperone, immunomodulation and cell proliferation and differentiation	(Jia *et al*. 2011; Kumar *et al*. 2015)
HSP 20	Plasma membrane	These protein chaperones protect other various proteins against denaturation by heat and aggregation.	(Kumar *et al*. 2017)
HSP27	Cytosol	Maintenance of muscle structure and function	(Kammoun *et al*. 2013; Liu *et al*. 2010; Min *et al*. 2015; Archana *et al*. 2017)
HSP 40	Cytosol	Act as a cofactor of other proteins, especially HSP70	(Danwattananusorn *et al*. 2011)
HSP 60	Mitochondria	Protein homeostasis	(Alyamani 2020; Singh *et al*. 2018; Kumar *et al*. 2015)
HSP 70	Cytoplasm	Protein folding and increased production because of stress or starvation	(Maibam *et al*. 2017; Banerjee *et al*. 2014; Bharati *et al*. 2017; Khan *et al*. 2020; Min *et al*. 2015; Archana *et al*. 2017)
HSP 90	Cytoplasm	Controls the cell cycle and survival, hormonal activity, and other various signaling pathways	(Aritonang *et al*. 2017; Deb *et al*. 2014; Hahn 1999; Khan *et al*. 2020; Kumar *et al*. 2015; Min *et al*. 2015; Archana *et al*. 2017)
LEF1	Nucleus	Hair cell differentiation and follicle morphogenesis	(Gao *et al*. 2017; Flori *et al*. 2019)
MAPK	Cytosol	Activates response to excitotoxic stress	(Sigdel *et al*. 2019)
PRLR	Plasma membrane	Development of sleek hair in cattle	(Hansen 2020)
RAB39B	Plasma membrane	Involved in vesicular trafficking	(Jiang *et al*. 2019)
TCF7	Nucleus	Transcriptional activator involved in T-cell lymphocyte differentiation	(Flori *et al*. 2019)
UBE2I	Nucleus	Targets abnormal or short-lived proteins for degradation	(Jiang *et al*. 2019)

During this THI, the rectal temperature and respiratory rates rose notably, and the serum concentration of HSF, HSP27, HSP70 and HSP90 was higher. This result shows that HSP is a valuable indicator of animal heat stress and can be used as a biomarker in dairy cows' adaptation to harsh environments.

Blood parameters, serum T3, cortisol and HSPs (HSP27, HSP70 and HSP90) levels were tested in a similar study in Hanwoo Steer (Korean cattle) under heat stress conditions (Baek *et al*. 2019). Also, the mRNA expression studied of HSPs genes in the liver tissue of cattle. Two-level conditions of THI were administrated to cattle in respiratory chambers. The first level (control) was maintained at thermoneutral conditions (THI=64); in the second level, a THI of 87 was maintained to create harsh environmental conditions for cattle. As expected, the cattle's body temperature, rectal temperature, and respiratory rate were markedly raised during harsh environmental conditions. The feed intake and body weight were also recorded, which decreased during HS than control conditions. There was only increased HSP expression and concentration during high THI. The upregulation of HSP27's expression was 3.1- and 6.6-fold change after 3 and 6 days, respectively. Similarly, the fold change increase in HSP90 was 2.3-fold and 5.6 fold after 3 and 6 days, respectively. The highest increase in

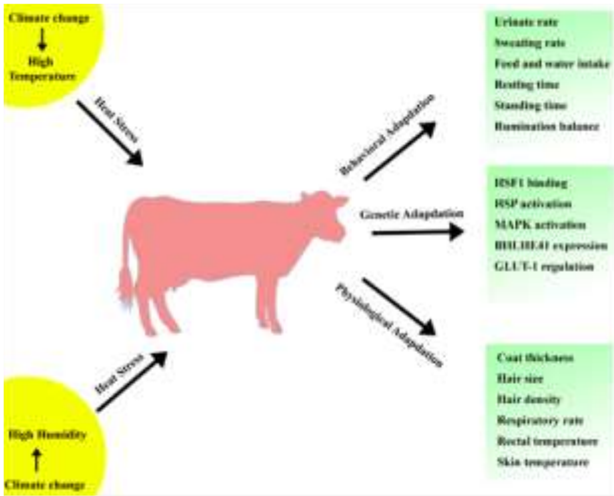

Fig. 1: Cattle response to heat stress and adaptation

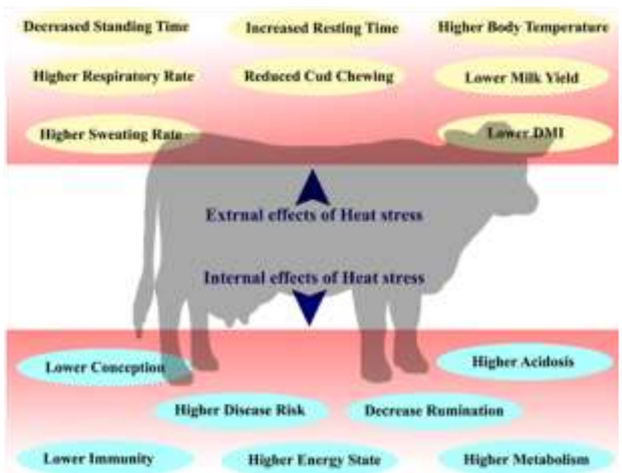

Fig. 2: External and internal heat stress effects on cattle's body

expression was found in HSP70, 9.2 and 16.7 folds after 3 and 6 days, respectively. The increased expression of HSPs in Hanwoo cattle indicates that the cattle are better adapted to heat stress conditions.

Heat shock protein 40

HSP40 is also known as DnaJ Heat Shock Protein Family (Hsp40) Member A1 because of its association with HSPA8 regulation, J-domain facilitator and binding ability to the N-terminal of the ATPase domain (Minami *et al*. 1996). It is also important in chaperone function and repairing damaged proteins due to stress conditions (Hartl and Manajit 2002). In addition, there has been a notable ~7-fold increase in ATPase activity in the presence of HSP40. This notable increase allows proper renaturation of proteins which thermally denatured conditions may cause.

The C-terminal and N-terminal regions of HSP40 have been explored to find any association with heat adaptation

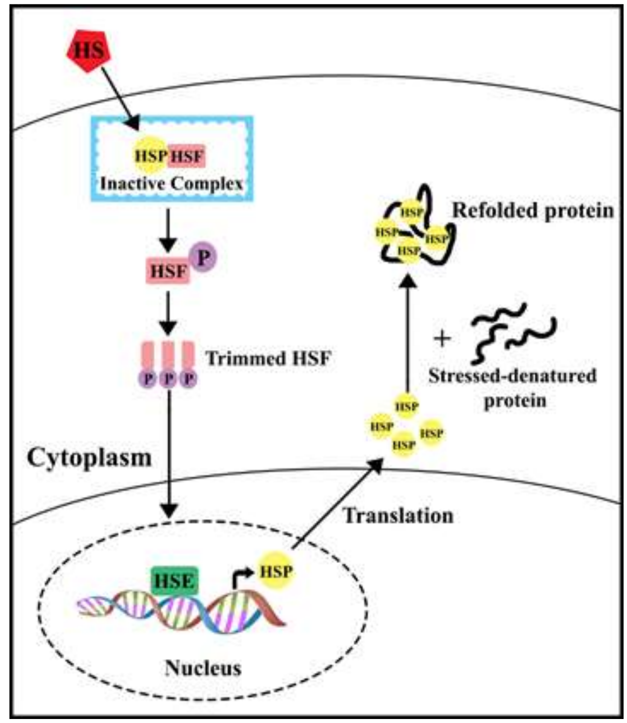

Fig. 3: HSP Pathway activation in heat stress conditions

(Ajayi *et al*. 2018). Mutations in these regions can disrupt the chaperone's functions under cellular stress. The study was conducted on cattle and yak from Nigeria, Pakistan and the USA. The N-terminal region of Asian, African, and USA breeds showed 11, 9 and 2 haplotypes, respectively, whereas the C-terminal region was conserved in all the studied animals. The sequence analysis of the N-terminal (J domain) detected five polymorphic loci. A total of three mutations occurred in exon 2 of all three breeds, while the remaining mutations occurred in exon 3 of African and Asian cattle breeds only. The difference in polymorphic loci of American cattle may be because of its moderate environmental conditions, whereas the other two cattle breeds experience tropical environments. It is noteworthy that the study cannot conclude whether the mutations are because of any environmental stress conditions, but further investigation of the HSP40 gene can solve this mystery.

Animal blood regulation can be effectively studied to examine the physiological adaptation to environmental stress. Such a study was conducted on the blood leukocytes of Holstein-Friesian (HF), Sahiwal cattle and Murrah buffaloes (Kishore *et al*. 2014). The study determined the role of HSPs (HSP40, HSP60, HSP70, and HSP90) in peripheral blood mononuclear cells (PBMCs) during high temperatures (~42^{0}C). PBMCs of HF were more affected by heat shock treatment and caused sudden heat loss as compared to other breeds. The qRT-PCR results showed a significant increase in the expression of HSP70 and HSP60. However, the expression levels of these genes varied, as buffalo had the highest expression of HSPs than cattle.

The HSP40 differential expression has been investigated in bovine embryos: degenerates and blastocysts (Zhang *et al*. 2011). The study tested the expression of HSP40 as it plays a significant role in the assembly of protein when a cell is under different stress conditions. During bovine embryo development, the degenerate embryos are under stress, which may disturb protein homeostasis; thus, the expression of HSPs was investigated in bovine to find any helpful information. The expression of HSP40 was significantly high in degenerate embryos, up to an average of 7.6-fold compared to blastocysts. The upregulation of the gene confirms its vital role in maintaining proteostasis in a stressful environment.

Heat shock protein 60

HSP60 is another essential heat shock protein and is known as a chaperonin. The protein translocates, folds and assembles different native proteins in various organisms under stress conditions (Langer and Walter 1990). The most important aspect is that the HSP60 protein is an intra-mitochondrial molecule that assists in protein folding and prevents misfolding during HS conditions.

The change in the expression of HSP60 and GLUT-1 was investigated in buffaloes (Chilika (CH), Paralakhemundi (PM) and Murrah (MU)) during moderate and high THI (Singh *et al*. 2018). The study aimed to determine if the subjects (having dark skin colors and poor sweat glands) are better adapted to heat stress conditions and high milk productivity (lactose synthesis from glucose) using qPCR. Previously, GLUT-1 has also been associated with heat stress in cattle (Baumgard and Jr Robert 2013). The results show no significant increase in the relative expression of HSP60 in all breeds, whereas GLUT-1 showed high expression in MU (3.53-folds) compared to PM and a 4.41-fold increase compared to CH at moderate THI. GLUT-1 expression results may be valuable since the production of milk is predominantly affected when animals undergo harsh environmental conditions.

The negative effect of HS also damages fetal development in the bovine uterus. Therefore, the mRNA expression of HSPs (HSP27, HSP60, HSP70 and HSP90) has been studied in uterine endometrial tissues of Holstein dairy cows in summer (avg. THI=73) and winter (avg. THI=42.4) (Bai *et al*. 2020). The qPCR analysis showed lower mRNA expression ($p < .05$) of all HSPs (except HSP70) during summer as compared to winter. The lower expression of HSPs may be due to variations in heat stress conditions in vitro and in vivo systems. Further studies on protein expression will help comprehend HSPs' role under heat stress in bovine uterine endometrial tissues.

Heat shock protein 70

HSP70 is an essential heat shock protein produced in almost all organisms and is functional in multiple cells. Its vital role is to interact with peptide segments and folded proteins to cause intense folding and aggregation during heat and chemical stress.

Several novel polymorphisms have been detected in the untranslated region (UTR) and coding region of HSP70 (Sodhi *et al*. 2013). The Indian Zebu cattle (indicine and taurine) and four riverine buffalo (bubaline) were studied to find polymorphism in the tropical adaptation of these subjects. The coding region of HSP70 was similar in cattle and buffalo. In contrast, there was a ~200 nucleotide increase in the UTR's length of buffalo. A total of 50 SNPs and 4 INDELs were detected in cattle (taurine and indicine) and buffalo. A total of 15 SNPs (6 at 5′flanking region and 9 in the coding region) were detected among buffalo breeds, while the 3′-UTR of cattle and buffalo were monomorphic. The results show some novel polymorphism in potential transcription factor binding domains and microsatellites, which may be used as a molecular marker for thermotolerance.

The qPCR analysis of mRNA expression in Tharparkar cattle during HS shows a significant increase in the HSP70 gene (Bharati *et al*. 2017). The animals were kept for 50 days under thermal conditions. The HSP70 expression was found significantly higher after 15 days of heat exposure and decreased later. The expression gradually increased again on the 32^{nd} day, suggesting a two-level alarm system for double protection against heat stress conditions.

Similarly, the expression levels of various HSP70 genes (HSP70.1, HSP70.2 and HSP70.8) have been investigated under different seasonal conditions (winter, summer and spring) in the skin of Zebu (Tharparkar) and crossbreed (Karan Fries) cattle (Maibam *et al*. 2017). The qPCR analysis revealed the gene expression of constitutive (HSP70.8) and inducible (HSP70.1 and HSP70.2) higher in summer than in winter and spring. The HSP gene expression was 4.92±0.53 in Tharparkar and 3.01±0.30 in Karan Fries during summer. The inducible HSP gene expression was 6.86±0.30 and 4.01±0.18 in Karan Fries and Tharparkar during summer. The skin and rectal temperature increased during summer in both subjects. The higher expression of HSP70 during summer in cattle shows its potential role during heat stress conditions.

Heat shock protein 90

The role of HSP90 has been widely studied and is recognized as a chaperone and assists in folding and stabilizing other proteins remarkably during heat stress conditions. It also plays a vital role in degrading other proteins (Blagg and Timothy 2006). The HSP90 is also produced in cells exposed to other stress and heat, such as dehydration (Hahn *et al*. 2011).

In an interesting study, the gene expression of HSP90 was compared in vitro and under environmental heat stress (37–45C) in Sahiwal and Friswal cattle (Deb *et al*. 2014). The cattle's PBMC were exposed to heat for one hour at 42°C and tested for HSP90 relative expression along with peak summer sessions. A higher expression level of HSP90 was observed in Sahiwal (3.29 ± 0.49) than in Friswal (2.11 ± 0.38) cattle during in vitro heat stress. Similarly, protein concentration was significantly higher in Sahiwal (4.13 ± 0.48 ng/mL) than in Friswal (2.98 ± 0.46 ng/mL). Furthermore, during peak summer environmental temperatures (at 45°C), the relative expression of Sahiwal (3.67 ± 2.99) was higher than the Friswal (2.98 ± 2.52) cattle breed. Hence, this shows that Sahiwal cattle adapt more to heat stress than Friswal under in vitro and environmental heat stress conditions.

(Pires *et al*. 2019) studied the HSPs (HSP60, HSP70 and HSP90) relative expression, physiological behavior (rectal temperature (RT), heart rate (HR), respiratory rate (RR), skin temperature (ST)) and cortisol concentration in Brazilian dual-purpose cattle (Nelore and Caracu) during HS. The three HS conditions were direct sun contact (THI = 90.79), under shade (THI = 82.17) and morning (THI = 82.67). The Caracu cattle maintained the physiological response (RT = 40.40, HR = 114, RR = 76 and ST = 47) in all conditions compared to Nelore (RT = 39.90, HR = 110, RR = 70 and ST = 44.36). The mean cortisol level was 23.74 ng/mL and 18.52 ng/mL in Caracu and Nelore, respectively. The mean relative expression of HSP60, HSP70 and HSP90 in Caracu was 2.99, 1.93 and 1.18, respectively. Contrastingly, the mean relative expression was 2.76 (HSP60), 1.98 (HSP70) and 1.55 (HSP90) in Nelore. The monthly relative expression of HSP60 showed higher expression during October and February in both breeds, whereas HSP70 had higher expression in December and lowest in February in both breeds. The HSP90 showed higher expression during October and December. In conclusion, the study identified a unique pattern of responses to heat stress in both breeds and their adaptation to tropical climates.

Conclusion

This review highlighted multiple studies conducted to investigate the HSP's role in cattle. The expression level of these genes depends on environmental conditions and varies in different breeds. The HSPs exhibit a unique physiological function in stress conditions and are activated by the HSP activation factors that start their transcription and translation. The studies on the genetics of HS highlight another technique, gene editing, which will provide prospects of decreasing the heat stress on cattle and make them heat tolerant to harsh environmental conditions.

Furthermore, the economic loss because of climate change and its effect on heat stress is very high. Breeding programs for heat-tolerant cattle can be adjusted to accelerate and improve environmental conditions through proper management, reducing global warming and minimizing the greenhouse effect in the environment. Since controlling the environment is not a single-handed task, different organizations and institutes should collaborate and find valuable solutions. Working in this manner will provide high valued input to tackle the global problem of heat stress in cattle.

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Author Contributions

TH conceived the idea, QRQ and TH drafted and prepared the manuscript, AW and TH performed the critical revision of the article. MEB provided the critical insight and revisions. All authors gave necessary suggestions, revised and approved the final manuscript.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability

Not applicable.

Ethics Approval

Not applicable.

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