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A Review on Thermoregulatory Responses in Tharparkar Cattle against Heat Stress

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ABSTRACT

In changing climatic scenario, heat stress has become one of the most important challenges faced by dairy industry today. To maintain appropriate microclimate in animal houses i.e., sufficient air circulation, temperature, humidity, low pollution and low content of gases have been major factor to concern. These factors significantly contribute to the proper development and maintenance of cattle welfare and subsequently livestock-based food security. India ranked fifth in the Global Climate Risk Index, 2019 and extreme heat has potentially deadly effects of climate change, especially for populations living in the tropics. Dairy cattle show heat stress when the temperature humidity index (THI) is higher than 72 (Armstrong, 1994). Their threshold for heat tolerance depends on the genotype as well as production level. Animals on higher production levels tend to be more sensitive to heat stress. Indigenous evolved crossbred cattle like Karan Fries, had higher metabolic heat production, methane, energy loss and physiological responses as compared to zebu cattle. The lower metabolic rate of zebu breeds indicates better adaptability of it to tropical climatic condition in terms of heat and methane production. Among, Indigenous cattle breeds Tharparkar exhibits more tolerance to heat stress then breeds like Sahiwal, Gir, Red Sindhi and crossbreds. Thermoregulatory responses play major role in conferring thermotolerance against heat stress through expression of highly conserved family of proteins known as heat shock proteins (HSPs). Despite these thermoregulatory responses toward heat stress prodigiously muddles Zebu cattle Tharparkar's productivity as compared to other indigenous and crossbred cattle.

HIGHLIGHTS

- Study of thermoregulatory responses to identify climate resilient animals for food security.
- Documenting responses of Tharparkar cattle as adaptive response against heat stress.

Keywords: Heat stress, Tharparkar, Molecular Response, Thermotolerance

The global temperature is expected to increase by 1.5°C or more (IPCC AR6, 2021) in coming 20 years. In the past century the surface temperature has increased all over Asia. In South Asia; India and Pakistan are the most vulnerable to climate change. India ranked fourth among the list of countries most affected by climate change in time span of 1996 to 2015 (Kreft, 2016). Effects of climate change are perceived as a major challenge to the sustainable livestock production. Heat stress is among the most concerning and potentially deadly effects of climate change. The livestock-based food security is threatened due to reduced milk yields, milk quality, meat production and fertility in the country. Livestock production is likely to be adversely affected by climate change. Livestock plays an important

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role in Indian economy, as it contributes 4.11% to total GDP and 25.6% of total Agriculture GDP (BAHS, 2022).

India stands first in milk production in the world accounting for 20.6 per cent of world production with an annual output of 198.44 million tones and stands eighth in meat production as production in the country has increased from 6.69 million tonnes in 2014-15 to 8.80 million tonnes in 2020-21 (NDDB, 2020). Buffaloes and crossbred cattle produce the major portion of total milk production. But Zebu cattle remain the sole milk producer in arid region where environmental temperature ranges between 0°C to 50°C and less availability of feed and fodder resources.

In tropical and subtropical regions more than 4ºC increase in ambient temperature than average during scorching summer, severely upsets production and productivity. Specially the tropical zone is more susceptible to thermal stress as the temperature during peak summer ranges from 28°C to 44°C which is highly deleterious and life threatening to livestock while in most of the developing countries this stress provokes a decline around 25% in production and productivity (Upadhyay *et al.,* 2010; Yadav *et al.,* 2016). Amongst all the climatic variables, ambient temperature plays a paramount role affecting livestock's reproduction and production (Das *et al.,* 2011; Mishra *et al.,* 2013; Singh *et al.,* 2014). Basically, thermo-neutral zone (TNZ) temperature is higher for zebu cattle breeds in India. Global warming has directed livestock research towards exploring climate-resilient livestock breeds and their responses to thermal stress. However, most livestock are naturally adapted to the adverse effects of heat stress in a particular agroclimatic region (Mehla *et al.,* 2014; Kishore *et al.,* 2014). In India among milch cattle breeds Tharparkar cattle shows exceptional high performance in terms of milk production and reproduction during elevated ambient temperatures-humidity and that could be incorporated into heat abatement management decisions. More research is needed to identify improved heat tolerant characters of this breed and subordinate thermo tolerant cellular and molecular mechanisms to climatic stressors. These resilient characters to adverse climatic conditions can be incorporated for genetic evaluation and selection programmes in cattle.

The cellular response to heat stress in mammalian organisms is controlled at the transcription level and it is mediated by a family of heat shock factors (HSFs), heat shock element (HSE) and HSPs (Singh *et al.*, 2020). The HSPs have chaperone activity ensuring the folding, unfolding and refolding of stress-denatured proteins. The most commonly studied HSPs in farm animals are HSP70, HSP90 and HSP27. Up regulation of HSF1, HSF10, HSP10, HSP27, HSP40, HSP60, HSP70, HSP90 and activation of Ingenuity Pathway Analysis (IPA) revealed eukaryotic Initiation Factor 2 (eIF2) signaling pathway in Tharparkar and down regulation in crossbred represent molecular response for climate resilience characteristic of Tharparkar cattle under heat stress (Khan *et al*., 2020). The differential expression patterns of HSP90 have a role in long-term heat acclimation in this breed. Expression of HSP105 also indicates maintenance of homeostasis at higher temperature in Tharparkar cows. Higher expression of the antioxidants in Tharparkar enables it to cope up with higher levels of free radicals generated as a result of heat stress while Crossbred is unable to do so. This paper reviews the performance of the important Indian cattle breed Tharparkar in terms of its production, reproduction and associated heat stress responses at various levels.

Effects of heat stress in dairy animals

Heat stress is usually measured in the form of temperature humidity index (THI). When temperature humidity index (THI) reaches higher than 72 in dairy cattle, symptoms of heat stress become evident and the values of THI > 78 is considered as very severe heat stress (Armstrong, 1994). However, the threshold for heat tolerance depends on the genotype as well as production levels of dairy animals. High producing animals tend to be more sensitive to high temperature and humidity. Most of domestic animals maintain their physiological parameters within a narrow range. Both physiological and behavioural responses are involved in thermoregulation. In thermoneutral environmental conditions, animals are able to maintain their physiological parameters in equilibrium but in thermal exposed conditions physiological and behavioural responses change in intensity and duration in relation to genotype and environmental factors. Crossbred cattle are more prone to high ambient temperatures, which ultimately results in raised body temperature, respiration rate, heart rate and evaporative heat loss from skin and pulmonary tract. Zebu cattle are more heat tolerant due to their lower metabolic rate, a thinner coat and more efficient heat loss mechanism.

In the conditions of heat stress, the animals consume fewer quantities of feed in relation to their real needs (Joksimović-Todorović *et al.*, 2011). The quantity of feed intake could decrease by up to 20% in summer period in relation to spring period and when outdoor temperature reaches 40ºC, the consumption of food can decrease by even 50%, which disturbs the energy balance of animal and therefore, the activity of mammary gland. Heat stress decreases milk production by 10 to 30%, with significant reduction in fat and proteins in dairy cows (Seignalini *et al.*, 2011). When temperature rises above 30ºC, a decrease can be noticed in terms of the quantity of milk, fat content and protein content by up to 30%, from 3.6% to 3.2% and from 3.34% to 3% respectively. Heat stress significantly reduced the milk production, fat percent and proteins percent, but it had no effect on lactose content (Zheng *et al.*, 2009). A noticeable change was seen in milk quantity at varying temperature ranges *viz.* 35ºC by 33%, at 40ºC by 50% while 39.7% and 16.9% reduction in fat percent and proteins respectively, whereas seasonal variations were also noticed in the lactose content as later was reduced from 4.5% in spring to 4.43% in summer (Vuković, 2008). Heat stress is not only responsible for decrease in milk production, in terms of quantity and quality but also reduction in reproductive efficiency due to decreased oocyte and sperm viability, decrease in conception rate, and reduced fertility (Table 1).

Impact of heat stress in high yielding cows

High yielding cows are more susceptible to heat stress than low yielding cows, as feed intake and milk production increases thermoneutral zone shifts to lower temperature. Hence, heat stressed cow activates its physical and biochemical process to counter stress and to maintain thermal equilibrium. Thermal stress varies according to the breed (Table 2). The heat tolerance capacity of crossbred cattle is poor mainly due to less developed and low density of sweat glands. Moreover, factors such as milk production levels, the quantity and quality of feed, health status and hydration levels of the animal can strengthen the effects of high temperatures. Thus, for example, a high-producing cow (more than 30 kg/day) generates 48% more heat than a dry cow, thereby presenting a higher risk to suffer heat stress. Cows at the beginning of lactation are also more likely to suffer heat stress. The dramatic increase in heat

Table 1: Effects of heat stress on livestock (production and reproduction)

Parameter	Species	Heat stress	Reference
Milk production	Buffalo	Decrease	Das *et al.* (2016)
	Cattle		Baumgard *et al.* (2011)
	Sheep		Finocchiaro *et al.* (2005)
	Goat		Nardone *et al.* (2010)
Oocyte quality and growth	Cattle	Detrimental	Ronchi *et al.* (2001)
	Sheep		Sejian *et al.* (2012)
	Pig		Barati *et al.* (2008)
FSH and LH level	Buffalo	Decrease	Singh *et al.* (2013)
	Cattle	Increase	Khodaei-Motlagh *et al.* (2011)
Estradiol	Cattle	Decrease	Wolfenson *et al.* (2000)
Fertility	Cattle	Decrease	Singh *et al.* (2013)
	Pig		Nardone *et al.* (2010)
Pregnancy rate	Buffalo	Decrease	Dash (2013)
	Cattle		Sejian *et al.* (2012)
			Schuller *et al.* (2014)
Embryo development	Pig	Impaired	Nardone *et al.* (2010)
Sperm concentration and quality	Poultry	Lower	Mathevon *et al.* (1998)
	Bulls		Balic *et al.* (2012)
	Boars		Bhakat *et al.* (2014)
			Kunavongkrita *et al.* (2005)

Table 2: Breed wise changes in milk composition and milk yield due to heat stress

Species	Milk production level	Milk composition	References
Holstein-Friesian	Milk yield decreased	Reduction in protein concentration casein number and casein concentration	Cowley *et al.* (2015)
Jersey	Increase in milk yield compared to Holstein	Reduction in fat and protein content	Smith *et al.* (2013)
Tharparkar	No significant yield reduction	No significant change in SNF and fat	Alhussien *et al.* (2016)

Table 3: Surpassing responses of Tharparkar cattle as compared to other breeds in combating heat stress

Parameter	Compared with	Reference
Circadian physiological responses and blood ions	Karan Fries	Banerjee and Ashutosh (2011b)
Diurnal rhythms of physiological parameters		Banerjee and Ashutosh (2011a)
Skin pigmentation (MCIR and PEML)		Maibam *et al.* (2014)
Dermal fibroblasts		Singh *et al.* (2014)
Physiological, haematological and hormonal parameters		Indu *et al.* (2016)
Dio2 and TRIP11 gene		Naidu (2016)
Skin protective mechanism, Caspases and HSPS		Maibam *et al.* (2017)
Physiological, hematological and behavioral profile		Pandey *et al.* (2017)
Milk yield		Singh *et al.* (2019)
miRNA-based biomarkers		Kumar *et al.* (2021)
ATP1A1 gene	Vrindavani	Kashyap *et al.* (2014)
Genome integrity	Sahiwal and Kankrej	Kumar *et al.* (2016)
Skin temperature, blood flow and physiological functions	Sahiwal and Karan Fries	Singh *et al.* (2017)
Mammary immunity	Gir and Sahiwal	Alhussien and Dang (2018)
Growth, Milk production and composition	Tharparkar - Light v/s Dark coat colour	Prabhakar *et al.* (2018) Rashid *et al.* (2019)
Hormone responses and antioxidant enzyme	Sahiwal and crossbred (Hariana × Holstein Friesian /Brown Swiss/Jersey)	Tejaswi *et al.* (2020)
Genetic diversity	Bovine SNP50 BeadChip	Saravanan *et al.* (2020)
Transcriptome profiling	Vrindavani	Khan *et al.* (2021)
Unique SNPs/QTL for production traits	Taurine	Kumar *et al.* (2021)
Disease resistance and thermotolerance genes	Taurine	Saravanan *et al.* (2021)
Microsatellite Analysis for breed specific clustering	Rathi, Nagori, Mewati, Gir, and Kankrej	Sodhi *et al.* (2011)

production by the animal is due to both an increase in milk production and food ingestion.

Adaptation of Tharparkar cattle to heat stress

Tharparkar cattle shows better adaptability in arid region to heat stress due to light coat color, lower coat scores and lower hair densities and perform better in terms of live body weight gain, milk production and reproduction efficiencies. This could partly be attributed to the fact that light colored cattle had lower values of skin temperature, rectal temperature and respiration rate which indicates better thermoregulatory ability and lesser heat stress in these animals as compared to dark colored cattle (Prabhakar *et al.*, 2018; Rashid *et al.*, 2019). Exotic and crossbred (Karan Fries) animals had higher metabolic heat production, methane energy loss and physiological responses as compared to zebu (Tharparkar) cattle due to greater metabolic rate, which impart higher greenhouse gases to the environment. The lower metabolic rate of zebu breeds indicates the better adaptability of it to tropical climatic condition in terms of heat and methane production (Kumar *et al.*, 2018). Tharparkar breed has higher endurance power as compared to other cattle breeds (Table 3) which are important for economic safety of engaged rearing community.

Thermoregulatory responses in Tharparkar cattle against heat stress

The average THI values in India were the highest for summer (84.34) followed by spring (68.25) and lowest for winter (52.72) season. The THI in summer season exceeded 72, *i.e.*, the reported threshold value of THI for dairy cattle, thus imposing heat stress. In summer, the highest values for RT, RT, ART and ARR at 2 pm while the lowest value for HTC at 10 am indicated heat stress (Bhat *et al.*, 2016). Heat stress can make changes in the feeding pattern, rumen function and udder health, which ultimately leads to decreased milk production. An inability of organism to adapt to newly created situation leads to health disturbance, reduction in nutritive needs and milk production, change in chemical composition of milk and reproductive disorders.

Behavioral responses

Behavioral changes were observed with changes in temperature and CO_2 levels. Animals show more nervousness, restlessness, salivation, profuse tongue protrusion and panting. Panting is observed when the normal heat dissipation mechanism is compromised, and it culminated into evaporative cooling as the most effective means of heat loss (Table 4). Animal spend most of the time standing with the increase in stress level due to rise in temperature and CO_2 levels (Pandey *et al.*, 2017). Restlessness, open mouth breathing, panting, tongue protrusion, frothy salivation and muzzle secretion had seen to be shifted from absence to highly increased response for all of these behavioral parameters in effect of elevated temperature and CO_2 levels from 25 to 45ºC and 400 to 600 ppm respectively in Tharparkar cows (Pandey *et al.*, 2017).

Heat stress also results in decreased feed intake and increased water intake in dairy cattle. The consumption of high quantities of food results in the increase of metabolic increments which require efficient thermoregulatory mechanisms in maintaining body temperature and physiological homeostasis. During heat stress dairy cows not only consume less food but also the utilization of some food ingredients is reduced (Rhoads *et al.*, 2009). It is rather complicated to determine precisely the moment when the cow enters into the heat stress because the incidence of heat stress is not only influenced by energy balance but also by a quantity of water and metabolism of sodium, potassium and chlorine. The decrease in milk production under heat-stress situations is directly linked to a reduction in feed intake, while the energy needs of the animal increases. The intake of food is the most optimal in the early morning and late in the evening since the digestion of food reaches its peak 3 to 4h after food intake while in this way the hottest part of the day is being evaded. A study on Tharparkar calves reported that Mean ± SE for DMI (Kg/Whole body weight) were observed as 2.65±0.03, 2.58±0.01 and 2.57±0.02 and water intake (Litres/day) 3.98±0.06, 6.35±0.16 and 7.71±0.25 at control (25°C), moderate (31°C) and severe (37°C) heat stress period, respectively (Jose *et al.,* 2020).

Physiological responses

Heat stress causes changes in the normal physiology of animals which is reflected by increase in rectal temperature, respiration rate, pulse rate, peripheral temperatures, stress enzyme (SOD and catalase) levels, decrease in blood electrolyte (sodium and potassium) concentration, decrease in PCV and haemoglobin levels (Banerjee and Ashutosh, 2011b). However, the change in physiological

Table 4: Behavioral responses in Tharparkar cattle during heat stress

Behavioural responses	Heat stress	References
Dry matter intake	Decrease	Banerjee and Ashutosh (2011a) Jose *et al.* (2020)
Water intake	Increase	Banerjee and Ashutosh (2011a) Pandey *et al.* (2017) Jose *et al.* (2020)
Standing time, Restlessness, Open mouth panting, Tongue protrusion, Frothy salivation and Muzzle secretion	Increase	Pandey *et al.* (2017)

Table 5: Physiological responses in Tharparkar during heat stress

Physiological responses	Heat stress	References
Rectal temperature, Skin temperature, respiration rate, heart rate and pulse rate	Increase	Indu, B. (2014) Kashyap *et al.* (2015) Bharati *et al.* (2017a) Bhat *et al.* (2016) Naidu (2016) Maibam *et al.* (2017) Pandey *et al.* (2017) Aggarwal *et al.* (2021) Singh *et al.* (2019) Khan *et al.* (2020)
Blood electrolytes		
Na and K	Decrease	Banerjee and Ashutosh (2011b)
Antioxidant enzymes		
SOD (Unit/min/g. Hb) and catalase (mmol of H_2O_2 consumed/min/mg Hb)	Increase Decrease	Singh *et al.* (2013) Maibam *et al.* (2017) Khan *et al.* (2020) Tejaswi *et al.* (2020) Choudhary *et al.* (2020)
GPx and ROS	Increase	Singh *et al.* (2013) Maibam *et al.* (2017) Tejaswi *et al.* (2020)
Blood parameters		
PCV	Decrease	Banerjee and Ashutosh (2011b)
Hb (g/dl)	Decrease	Indu, B. (2014) Pandey *et al.* (2017)
TEC (×106/µl) and hematocrit (%)	Increase	Indu, B. (2014) Pandey *et al.* (2017)
TLC (×103/µl)	No change Decrease	Indu, B. (2014) Kolli *et al.* (2014) Pandey *et al.* (2017) Alhussien and Dang (2018) Tejaswi *et al.* (2020)
pH and PCO_2	Increase	Pandey *et al.* (2017)
PO_2 and Base excess (BE)	Decrease	

parameters are lower in Tharparkar heifers than in Karan Fries heifers which indicate the greater thermotolerance capacity of this breed compared to crossbred cattle. Heat stressed cattle may try to reduce the body heat through thermoregulatory mechanisms which in turn affect feed conversion efficiency and lead to decreases in milk production (Table 5). By emitting the excess heat by way of evaporation there will be a significant loss of electrolytes especially when the outdoor temperature is above 35ºC so the recommendations of the National Research Council (1989) are to increase the quantity of sodium from 1.2 to 1.5%, chlorine from 0.4 to 0.6% and magnesium from 0.3 to 0.35% in dry matter. It is also necessary to increase the content of some vitamins in rations, especially the vitamins A (100000 IU/day), C (50000 IU/day) and E (500 IU/day). Lymphocyte proliferation and phagocytic index (LPA and PA) also decline due to immune cell reactivity and the higher susceptibility of infections during summer in crossbred when compared to native cows (Tejaswi *et al.,* 2020). In the conditions of high external temperatures, the emission of heat by conduction, convection and radiation decreases, while an evaporative emission of heat by sweating and panting increases to considerable degree. Above all thermal exposed period also comparatively affect the normal mean values ($P < 0.01$) and rate of body parameters in Tharparkar (Banerjee and Ashutosh, 2011a).

Neuro-endocrine responses

In summer season indigenous cattle, particularly Tharparkar, exhibited more tolerance to heat stress than other Zebu and crossbred cattle and higher amount of reactive oxygen species leads to oxidative stress status *viz.*, higher levels of reactive oxygen species (ROS), (superoxide dismutase (SOD), glutathione peroxidase (GPx) and HSP70s indicated greater sensitivity to heat stress (Tejaswi *et al.,* 2020). All these indicates strong neuro-endocrine responses of Tharparkar cattle in thermal stress conditions (Table 6). A significant increase in T3 level triggered metabolism which causes increase in heat production leads to rise in rectal temperature of Crossbred as compared to Tharparkar indicates an effective regulatory mechanism in modulating T3 levels in Tharparkar in response to heat stress (Khan *et al.*, 2020). The significant increase in normal physiological parameters such as respiration rate, rectal temperature and T3 level in crossbreed cattle than Tharparkar cattle, suggests the comparative high tolerance capacity of this Zebu cattle breed to cope up with heat stress.

Molecular responses

Heat stress significantly triggers molecular thermoregulatory responses in Tharparkar cattle (Table 7). Thermo-tolerant gene expression and elevated heat shock protein (HSP) levels are observed to be the ultimate response through which the cell survives the heat stress. The HSPs have chaperonic activity ensuring the folding, unfolding and refolding of stress-denatured proteins. The components of heat shock response other than HSPs are heat shock factors (HSFs) and heat shock element (HSE). The cellular response to heat stress in mammalian organisms is controlled at the transcription level and it is mediated by a family of HSF which are regulated by the corresponding HSF genes. The activated HSFs bind with the HSE in the promoter region of HSP genes culminating in enhanced transcription of HSP mRNA (Velichko *et al.*, 2013; Mahat *et al.*, 2016; Somero, 2020).

Out of all HSFs, HSF-1 is the chief regulator of HSPs inside cellular system during heat stress. Heat stress activates HSF which forms trimer and translocates into nucleus. Inside the nucleus, HSF binds with heat shock

Table 6: Neuro-endocrine responses in Tharparkar during heat stress

Hormone	Heat stress	Author
Cortisol	Increase	Indu, B. (2014) Naidu (2016) Tejaswi *et al.* (2020)
T_3	Decrease Increase	Indu, B. (2014) Maibam *et al.* (2014) Khan *et al.* (2020) Tejaswi *et al.* (2020)
T_4	Decrease	Indu, B. (2014) Maibam *et al.* (2014) Tejaswi *et al.* (2020)
Prolactin, Dio2 and TRIP11	Increase	Naidu (2016)
GH	No change	Indu, B. (2014)
Ubiquitin-Proteasome System (UPS)- UBE2G1, UBE2S, and UBE2H	Increase	Khan *et al.* (2020)
CASP-3 and CASP-7	Increase	Maibam *et al.* (2017)
α-MSH	Increase	Choudhary *et al.* (2020)
MC1R, PMEL and Tyrosinase	Decrease	Maibam *et al.* (2014)

Table 7: Molecular responses in Tharparkar during heat stress

HSPs	Expression	Author
HSF-1	Increase	Kumar *et al.* (2015) Khan *et al.* (2020)
HSF-4 and HSF-8	Increase	Khan *et al.* (2021)
HSP10 and HSP60	Increase	Kumar *et al.* (2015)
HSP27	Increase	Archana *et al.*, 2017
HSP40	Increase	Alhussien and Dang (2018) Khan *et al.* (2021)
HSP70	Increase	Singh *et al.* (2013) In semen – Rajoriya *et al.* (2014) Singh *et al.* (2014) Kumar *et al.* (2015) Bhanuprakash *et al.* (2016) Maibam *et al.* (2017) Alhussien and Dang (2018) Choudhary *et al.* (2020) Khan *et al.* (2020) Shandilya *et al.* (2020)
HSP90	Increase	In semen – Rajoriya *et al.* (2014) Kumar *et al.* (2015) Bharati *et al.* (2017b) Alhussien and Dang (2018) Khan *et al.* (2020) Saadeldin *et al.* (2020) Singh *et al.* (2020)
HSP105	Increase	Indu, B. (2014)
NOS-isoforms	Increase	Singh *et al.* (2013) Bharati *et al.* (2017)
miRNAs	Increase	Kolli*et al.* (2014) Khan *et al.* (2020)
ATP1A1 gene	Increase	Kashyap *et al.* (2015)
Toll-like receptor (TLR) TLR2/4	Increase	Bharati *et al.* (2017b)
IL (Interleukins) IL2/6	Increase	Singh *et al.* (2013) Bharati *et al.* (2017b)
CD molecules	Increase	Alhussien and Dang (2018)

response element (HSE) located in the promoter region of DNA thereby regulates transcription of HSPs which is positively correlated with tolerance in many species (Driedonks *et al.*, 2015; Pires *et al.*, 2019; Kim *et al.*, 2020; Mishra, 2020). HSF1 is a positive transcription regulator of HSP70 and HSP90 and activation of eIF2 signaling pathway in Tharparkar (Khan *et al.*, 2020) during heat stress.

In general, HSPs are classified according to their molecular weight. HSPs with molecular weight less than 40 kDa are known as small molecule, *i.e.*, HSP10, HSP20, HSP22 and HSP27 (Bakthisaran *et al.*, 2015) and large HSPs like HSP40, HSP60, HSP70 and HSP90 (Kumar *et al.*, 2015). The most commonly studied HSPs in farm animals are HSP70, HSP90 and HSP27. All of these HSPs studied, HSP70 was recognized to be the ideal biological marker for heat stress in farm animals (Archana *et al.*, 2017; Hassan *et al*., 2019; Prihandini *et al*., 2022).

HSP10

The HSP10 increases mRNA expression in Tharparkar cattle during summer as an effect of heat stress (Kumar *et al.*, 2015; Kolli *et al.*, 2014).

HSP27

HSP27 is the most abundant small heat shock proteins across the farm animal species. This group of HSP is known to modulate cell growth, differentiation, redox state and tumorigenicity. The preferential expression of HSP confers transient thermal tolerance during heat and cold stress which is characterized by heat and cold response and adaptations associated with acclimatization. The HSP27 proteins indicate an increase with rising exposed temperature (heat stress) in Tharparkar cows (Archana *et al.*, 2017).

HSP40

Changes in the expression of the hub protein have a larger effect than change in expression of non-hub proteins in systems biology under heat stress. The hubs HSPA8 and HSPA1A are associated with regulation of nucleoporins genes and molecular chaperones viz. Heat Shock Proteins (HSPA5, HSPA4, HSPA12B, HSPA9 & HSP40), HSF1, Ubiquitin and Sirtuin. HSP40 has a noticeable increase under heat stress (Alhussien Dang 2018; Khan *et al.*, 2021).

HSP60

The up-surged mRNA expression of HSP60 during heat stress is a thermo resilient character in Tharparkar cattle (Kumar *et al.*, 2015).

HSP70

Heat stress triggers the transcription and translation of HSP70 gene in PBMCs of Tharparkar cattle. HSP70 functions as an intracellular molecular chaperone and plays a significant role in combating thermal stress and evokes thermo tolerance. The typical biphasic expression pattern of HSP70 could help to protect the animals by providing second window of protection and might be used as a biomarker of chronic heat stress in Tharparkar cattle. The serum concentration of eHSP70 and mRNA expression up regulated during heat exposure to defend the harmful effects of heat stress and might play an important role as a cryoprotective factor for PBMCs, thereby maintaining cellular homeostasis during heat stress in Tharparkar cattle (Bharati *et al.,* 2017a; Kolli *et al.*, 2014). The allelic variants of HSP70 gene reassociated with heat tolerability of the Tharparkar cattle. This gives the indication about the confirmation for having more variations conferring thermotolerance that may provide a chance of improving these breeds for higher thermo-tolerability (Bhat *et al.,* 2016). Lower expression of HSP70i mRNA and oxidative stress, and higher abundance of apoptotic enzymes to remove photo damaged cells in Tharparkar than Karan Fries cattle during summer indicates more thermotolerence of zebu cattle (Tharparkar) to summer heat stress (Maibam *et al.*, 2017). It may be a centrally important mechanism of zebu cattle for better adaptability to heat stress than crossbred cattle in tropical climate. The higher HSPA8 transcript in Tharparkar cattle compared to Sahiwal and Karan Fries cattle at 40^{o}C and 44^{o}C compared thermo-neutral zone at 37^{o}C (Kumar *et al.*, 2015; Singh *et al.*, 2014).

HSP90

The differential expression pattern of HSP90 attributed due to the fact that HSP90 might have a role in long-term heat acclimation in Tharparkar cattle (Bharati *et al.*, 2017b; Kolli *et al.*, 2014). HSP90 interacts with several protein kinases and transcription factors to either activate or degrade them, thereby playing a major role in signal transduction in many cellular systems (Pearl *et al.,* 2008).

HSP105

HSP105 (HSP105 and HSP5`), a major heat shock protein in mammalian cells, belongs to a subgroup of HSP70 family, HSP105/HSP110. HSP105, a high molecular weight mammalian stress protein is released in wide range of physiologic and pathologic responses to stress factors like heat, infection, ischemia, tumors and apoptosis (Saito *et al.*, 2007; Morris, 2002). Considerable elevation in HSP105 expression as compared to HSP27 and HSP90 indicates their role in maintaining homeostasis at higher temperature in Tharparkar cows (Indu, 2014).

Nitric oxide synthase (NOS) isoforms

Nitric oxide regulates vascular hemostasis, hematopoiesis, and immune response by modulating signaling, gene expression, and balance between proliferation and differentiation (Lapidot and Kollet, 2020). A definite interrelation might exist between HSP90, iNOS and eNOS (inducible and endothelial NOS) as the expression is significantly up regulated during long-term heat exposure (LTHSA) in summer season (Bharati *et al.*, 2017b).

Antioxidant level in heat stress

The ability to balance the ROS and antioxidant level is one of the key factors that would determine the tolerance of an individual to heat stress (Khan *et al.*, 2020). The antioxidant triad of GPX, SOD, and CAT that forms the first line of defense against reactive oxygen species (Lee *et al.*, 2008; Ighodaro and Akinloye, 2018) was found upregulated in Tharparkar and downregulated in Crossbred. Additionally, genes belonging to Peroxiredoxins - PRDX3, PRDX5 and PRDX6 that catalyzes the reduction of hydrogen peroxide and organic hydroperoxides (Yamashita *et al.*, 1999; Knoops *et al.*, 1999; Chen J-W *et al.*, 2000) were also found upregulated in Tharparkar and were either downregulated or not-differentially expressed in Crossbred. Higher expression of the antioxidants in Tharparkar enables it to cope up with higher levels of free radicals generated as a result of heat stress while Crossbred is unable to do so.

Role of miRNAs in thermo-tolerance

miRNAs are family of highly conserved single-stranded non-coding RNA comprising around 22 nucleotides which depresses post-transcription by base pairing with their target mRNAs of respective genes (Mishra, 2020). miRNAs regulate various physiological processes such as cellular proliferation and differentiation, apoptosis, development, focal adhesion and biosynthesis of secondary metabolites (Sengar *et al.*, 2018a). This miRNAs target various molecules like HSPs, toll like receptors (TLRs) along with multiple ligands via several signaling pathways to regulate heat stress response, immune response, oxidative stress response and cellular apoptosis amongst livestock species (Sengar *et al.*, 2018b).

Transcriptome profiling

Transcriptome profiling by RNA-seq is the most common methodology to study the changes in systems biology (Khan *et al.*, 2020). RNA profiling based on next-generation sequencing enables to measure and compare gene expression patterns. The global transcriptome of Tharparkar and crossbred indicated differential response to heat stress as evident from the DEGs, that are either distinct to both or have a difference in expression. The numbers of DEGs in crossbred cows were found to be more than in Tharparkar suggesting a greater dysregulation in systems biology in crossbred cows. Among the dysregulated genes, the numbers of unregulated genes were more than the downregulated genes in both genetic groups. However, a contrast in expression was observed with 18.5% of upregulated genes in crossbred cows downregulated in Tharparkar and 17.5% upregulated genes in Tharparkar downregulated in crossbred cows. While exploring the DEGs at a functional level, it was found that most of heat shock genes were found upregulated in Tharparkar and downregulated in crossbred cows. The differentially expressed and higher functional annotation of genes in Tharparkar as compared to Vrindavani pinpointing the counteracting effects of heat stress in the systems biology (Khan *et al.*, 2021). Unlike Vrindavani, Tharparkar is not only endowed with higher expression of the scavengers (UBE2G1, UBE2S, and UBE2H) of misfolded proteins but also with protectors (VCP, Serp1, and CALR) of naïve unfolded proteins. Further, higher expression of the antioxidants in Tharparkar enables it to cope up with higher levels of free radicals generated as a result of heat stress. In this study they found relevant genes deregulated in Tharparkar in the direction that can counter heat stress.

CONCLUSION

Cattle are comfortable in thermo neutral conditions and are in stress in thermal exposed conditions so shade and cooling facilities should be provided during summer to withstand heat stress and to improve health and productivity. The effect of heat stress on dairy production should be minimized by combining strategies with a low investment cost and feasible in terms of handling and additional management. Before hot weather comes certain measures must be taken because dairy cows are very sensitive to heat stress: to protect cows from direct sun rays; to provide cooling by use of fans and sprinkle systems; to provide high quality food (adequate proteins, fats, minerals and vitamins); to feed cows several times a day by smaller rations during the colder periods of day; to clean the feeders in order to prevent the spoiling of ration and to provide unlimited quantities of clear, cold water.

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