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CANDIDATE GENETIC MARKERS ASSOCIATED WITH THERMO-TOLERANCE IN ANIMALS

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ABSTRACT

Global warming, due to the drastic change in climate leads to serious consequences and a major threat to the sustainability livestock production systems in near future. Inability of dairy animals to adapt these stresses can result in a reduction in feed intake, milk production and reproductive success. Most of the negative effects of heat stress on animal performance are based on physiological adaptations to regulate body temperature. Selection approaches to reduce heat stress in animals on body temperature regulation during heat stress could increase thermos-tolerance. Rectal temperature (RT) and respiration rate (RR) are the most sensitive physiological parameters of heat tolerance. There is QTL for RT in heat-stressed dairy cattle. So SNPs could prove useful in genetic selection and for identification of genes involved in physiological responses to heat stress. Taking into consideration seriousness of the matter the present review, focuses on the markers associated with thermo-tolerance in animals.

KEYWORDS: Selection, SNP, Marker, QTL

INTRODUCTION

Due to population exposure and short of agriculture land the demand for livestock products is expected to double by 2050.In this fast changing world, where people are more addicted to machineries and artificial climate control rooms. The natural resources are reducing day by day that leads serious global climate change. It is a big worry, as climate change is a threat to livestock production, because of the impact on quality of feed crop and forage, water availability, animal and milk production, livestock diseases, animal reproduction, and biodiversity. Environmental, psychological, nutritional, pathological and manage mental stressors are major threat to livestock production performance (Lindquist, 1986; Subjeck and Shyy, 1986; Lindquist and Craig, 1988; Zavyet al., 1992; Macario, 1995; Grandin, 1997; Isosaki and Nakashima, 1998). Inability of dairy animals to adapt these stressors can result in reduction in feed consumption rate, milk production and reproductive success rate (Fuquay, 1981; Cavestanyet al., 1985; Sharma et al., 1988; Bernabuccietal., 1999; West, 2003; Bryantsevet al., 2007; Collier et al., 2008).

In tropical and sub-tropical areas, heat stress is the major constraint on animal productivity. Global warming has a great impact on productivity of livestock (Marai and Haeeb, 2010).

The total livestock population in India is 299.6 million out of which cattle are 190.9 million and buffaloes are 108.7million. Sheep and goat population is 65.1 and 135.2 million respectively. India ranks first in the world in milk production (146.3 MT, www.nddb.org; faostat.org, 2012), annual meat production is 8.89 MT whereas poultry meat production is 3.04 MT, and egg production of the country is 78.48 billion eggs.

Economic Consequences of Heat Stress

India is currently losing nearly 2% of the total milk production amounting to Rs 2,661 crore, due to global warming among cattle and buffaloes (Upadhyay, 2008). Final Report of the Network Project on Climate Change (2004-07) predicted the annual loss of about 3.2 MT in milk production of cattle and buffaloes, due to thermal stress by the year 2020, costing more than Rs. 5000 crores (Upadhyay*et al.,* 2008). The United States livestock industry has an annual economic loss between 1.69 and 2.36 billion US dollars, due to heat stress, of which 50% is occurring in the dairy industry (St-Pierre et al., 2003).

Heat Shock Proteins

During the course of evolution, cells have developed complex dynamic mechanisms to respond to the many physiological and environmental insults they encounter such as heat, cold, oxygen and food deprivation (Feder and Hofmann, 1999; Bryantsev*et al.,* 2007; Brown Jr *et al.,* 2010). Analysis of these responses has led to the discovery of a highly conserved cascade of protein activation, in a process termed as the heat stress/heat shock (HS) response (Parsell and Lindquist, 1993; Sonna*et al.,* 2002; Collier *et al.,* 2006; Collier *et al.,* 2008). Heat shock proteins (HSP) are a group of proteins induced by heat shock, the most prominent members of this group are a class of functionally related proteins, involved in the folding and unfolding of other proteins. Their expression is increased, when cells are exposed to elevated temperatures or other stress conditions, such as infection, inflammation, exercise, exposure of the cell to toxins, starvation, hypoxia (Maio, 1999). This increase in expression is transcriptionally regulated. The dramatic upregulation of the heat shock proteins is a key part of the heat shock response and is induced primarily by heat shock factor (HSF) (Wu, 1995).

Heat Stress (HS) on Animals

HS affects the health of livestock by daunting direct or indirect effects in normal physiology, metabolism, hormonal, and immunity system. Heat stress is the result of animal heat load such that the animal is not able to maintain to homeostasis. Heat gain or loss of an animal is a function of convection (sensible heat exchange – this may add to heat gain if environment temperature exceeds body temperature) conduction (contact with a surface exceeds body temperature), evaporation (latent heat exchange), radiation (long and short waves), and respiration (sensible and latent heat exchange). Heat stress occurs, when any combination of environmental factors causes the effective temperature of the environment to be higher than the animal's thermo neutral zone (Armstrong, 1994). The effect of heat stress is aggravated when heat stress is accompanied by high ambient humidity.

Heat stress has a direct negative effect on the appetite centre of the hypothalamus to decrease feed intake of animal [11]. HS adversely affects milk quality and quantity in dairy animals; especially animals of high genetic merit

[42-46]. Reduced milk production up to 50% might be due to reduced feed intake, whereas, the rest may be due to metabolic adaptations to HS as HS response markedly alters post-absorptive carbohydrate, lipid, and protein metabolism a part of reduced feed intake (Baumgard and Rhoades, 2013). Increased in basal insulin levels, with improved insulin response in stressed cattle (Baumgard and Rhoades, 2013, Rhoades *et. al.* 2013, Rhoades *et. al.* 2010) and in ewes (Sejian*et. al.* 2010) were observed, that explains the shift in glucose utilization in non-mammary gland tissue, affecting milk synthesis (Rhoades *et. al.* 2013).

HS, reduces the length and intensity of estrus, besides increased incidence of anestrous and silent heat in farm animals (Kadokawa*et. al.,* 2012, Singh*et. al.,* 2013, Singhal*et. al.,* 1984). It increases ACTH and cortisol secretion (Singh *et.al.* 2013), and blocks estradiol-induced sexual behavior (Hein and Allerich, 1992). Heat stress magnitude also effect the multifactorial mechanisms, involved in reducing fertility of dairy animals. HS effects oocyte development, by affecting its growth and maturation. Thermal stress adversely affects the embryonic growth and survival in dairy animals. Heat stress also leads to embryonic death by interfering with protein synthesis (Edwards and Hansen, 1996), oxidative cell damage (Wolfensen*et. al.* 2000), reducing interferon-tau production, for signalling pregnancy recognition (Bilby*et. al.,* 2008) and expression of stress-related genes associated with apoptosis (Fear and Hansen, 2011).

Genetic Selection and Heat Stress Resistance in Animals

Current trends in genetic selection has severely eroded the genetic base, ignoring the diversity of the production milieu, importance of adaptation, production of multiple products and social value of the livestock. Unplanned genetic introgression and crossbreeding, has contributed to the greatest extent to the loss of indigenous breeds. The genetic mechanism influencing fitness and adaptation, is not well explored and adaptation traits are usually characterized by low heritability. Breeding indices should be balanced, by including traits associated with heat resilience, fertility, feed conversion efficiency, disease tolerance and longevity in addition to higher productivity, and give more consideration to genotype by environment interactions (GxE), to identify animals most adapted to specific conditions and natural stratification of breeds and species by climatic zones. Adapted animals for different environment need to be identified for breeding purposes. Recent successes like slick hair gene in cattle (Oslon*et al.*, 2003), halothane gene in pig (Smet*et al.*, 1996) asks for extensive efforts, for finding significant quantitative trait loci (QTL), for stress and exploitation of heat shock proteins (HSP). Implementation of marker-assisted breeding value estimation (MA-BVE) using dense genome map for the highest possible accuracy will be a welcome step (Naskar*et al.*, 2012). Rectal temperature (RT) and respiration rate (RR) are the most sensitive indices of heat tolerance among the physiological reactions studied (Verma*et al.*, 2000). Heat stress compromises production, fertility, and health of dairy cattle. One mitigation strategy is to select individuals that are genetically resistant to heat stress. Most of the negative effects of heat stress on animal performance are a consequence of either physiological adaptations to regulate body temperature or adverse consequences of failure to regulate body temperature. Selection for regulation of body temperature during heat stress could increase thermo tolerance. Genome wide association study (GWAS) for rectal temperature (RT) during heat stress in lactating Holstein cows and identify SNPs associated with genes that have large effects on RT. There is QTL for RT in heat-stressed dairy cattle. Various SNPs could prove useful in genetic selection and for identification of genes involved in physiological responses to heat stress (Dikmen*et al.*, 2013).

Heat shock proteins were first identified in 1962, in *Drosophila* salivary glands, after thermal and chemical exposures (Ritossa, 1962). He described puffs on the salivary gland chromosomes of a fruit fly, *Drosophila busckii*.

The puffs were shown to be associated with newly synthesized RNA. These puffs appeared quickly after a sub-lethal heat shock and once the heat shock were removed and the temperature of the cells returned to normal, the puffs disappeared. This study was the first to report a response to heat shock at the molecular level and this response was referred to as the heat shock response. The heat inducible chromosomal puffs were later identified to be sites of active transcription of genes encoding a group of proteins now referred to as heat shock proteins (Tissieres*et al.,* 1974). Cells have developed complex dynamic mechanisms to respond to the many physiological and environmental stresses during the course of evolution. This response as a universally conserved cellular defense program has been observed from bacteria to man. In fact, the response is considered to be the most highly conserved genetic systems described till date. Analysis of these responses has led to the discovery of a highly conserved cascade of protein activation in a process termed as the heat stress/heat shock (HS) response (Parsell and Lindquist, 1993; Sonna*et al*., 2002; Collier *et al.,* 2006; Collier *et al.,* 2008).

Heat shock response is observed, not only as a response to heat but also to other environmental stressors, such as cold, oxygen deprivation, amino acid analogs, oxidants, heavy metals, chemicals such as dinitrophenol and sodium salicylate; psychological stressors, such as handling of animals by unknown individuals for managemental purposes including weaning, branding and vaccination, transport and exposure to novel places; food deprivation as nutritional stressors; bacterial, viral or any kind of infection and physical injuries leading to pathological conditions (Ritossa, 1962; Lindquist, 1986; Subjeck and Shyy, 1986; Lindquist and Craig, 1988; Zavy*et. al.,*1992; Macario, 1995; Grandin, 1997; Isosaki and Nakashima, 1998). Because, so many different types of stress have been shown to elicit a heat shock response, the response is more generally referred to as the stress response and the proteins induced, stress proteins/Heat shock proteins (HSPs). Stress response includes activation of HSF1; increased expression of Hsps and decreased expression and synthesis of other proteins; increased glucose and amino acid oxidation and reduced fatty acid metabolism; endocrine system activation of the stress response; and immune system activation via extracellular secretion of HSP (Kruger and Benecke, 1981; Sierra and Zapata, 1994; Schneider, 2000; Collier *et al.,* 2006; Collier *et al.,* 2008). Stress/heat shock protein genes are important candidates, for the study of stress response. Candidate mammalian HSP their cellular location and function is given in Table 1 and Table 2, respectively.

Table 1: Mammalian Heat Shock Protein Families and Cellular Location

Heat Shock Protein	Cellular Location
Small Hsps (15-30 kDa) Family	
HSP27	Cytosol
HSP40 Family	
HSP40	Cytosol
HSP60 Family	
Hsp60	Cytosol, ER, Nucleus
HSP70 Family	
HSP72 (HSP70)	Cytosol, nucleus
HSP73 (Hsc70)	Cytosol, nucleus
HSP75 (mHSP70)/ Glucose-regulated protein75 (Grp75)	Mitochondria
HSP78/Grp78	Endoplasmic reticulum (ER)
HSP90 Family	
HSP90	Mitochondria
Large Hsps Family	
HSP110	Cytosol, Nucleus

(Leppa and Sistonen, 1997; Lindquist and Craig, 1988; Kregel, 2002; Concannon*et al.*, 2003)

Table 2: Function of Candidate Heat Shock Protein

Protein	Function	Reference
HSP27	Microfilament stabilization	Kregel, 2002
	Cellular antiapoptotic activity	Arrigo, 1994; Mehlen*et al.*, 1996; Samali and Cotter,1996; Garrido*et al.*, 1999; Wagstaff*et al.*,1999; Brueye*t al.*,2000;Tezel and Wax, 2000
	Increases cellular resistance against heat shock and other injuries such as those mediated by chemotherapeutic drugs and oxidative stress (e.g., tumor necrosis factor alpha)	Arrigo and Landry, 1994;Mehlen *et al*.,1997; Arrigo,1994; Rosse *et al.*, 1998
HSP60	Refolding of proteins and prevention of aggregation of denatured proteins, pro-apoptotic effects	Leppa and Sistonen, 1997; Kregel, 2002
HSP70	Molecular chaperone; Protection of cells from chemical and heat shock - cellular antiapoptotic activity	Samali and Cotter,1996;Sistonen and Leppa, 1997;Mosser *et al.*, 1997; Jaattela*et al.*, 1998; Li *et al*.,2000; Kamaruddin*et al.*, 2004
HSP90	Molecular chaperone; cellular antiapoptotic activity; regulation of steroid hormone receptors and protein translocation	Leppa and Sistonen,1997; Pandey *et al.*, 2000; Kregel, 2002
HSP110/104	Molecular chaperone Protein Folding; Thermotolerance	Leppa and Sistonen, 1997; Kregel, 2002

HSPs is detectable in almost all organisms, from prokaryotes to mammals (Arrigo and Mehlen, 1994; Concannon*et al.*, 2003). The limits between different families of HSPs, are not well defined and researchers in different disciplines may group families differently, however the families, defined by Leppa and Sistonen (1997), serve as a guide to organize known and new information on Hsps, classifying the major heat shock proteins, into six protein families identified by their molecular sizes (i) large HSPs (proteins exceeding 100 kDa); (ii) HSP90 family (proteins from 83 to 90 kDa); (iii) HSP70 family (proteins from 66-78 kDa); (iv) HSP60 family; (v) HSP40 family and (vi) small HSPs (proteins from 15-30 kDa). Small HSP families (sHSPs) also vary in size from 15-30 kDa and to date nine different members of this family have been identified (Table 3) (Ingolia and Craig, 1982; Arrigo and Welch, 1987; Klemenz*et al.*, 1991; Kato *et al.*, 1994; Iwaki *et al.*, 1997; Boelens*et al.*, 1998; Krief*et al.*, 1999; Kappe*et al.*, 2001; Concannon *et al.*, 2003).

Table 3: Members of sHSPs Families

Sr. No.	Member
1.	HSP27
2.	p20
3.	HSPB3
4.	MKBP/HSPB2
5.	HSPB8
6.	HSPB9
7.	cvHSP
8.	α-A crystallin
9.	α-B Crystalline

Proposed mechanisms of cellular protection for HSPs include their functioning as molecular chaperones to assist in the assembly and translocation of newly synthesized proteins within the cell and the repair and refolding of damaged (e.g. Stress-denatured) proteins (Kregel, 2002). HSPs is also found in the cell under normal conditions, i.e. non-stressful conditions such as HSP73, so called as constitutive protein (Hsc70), simply monitoring proteins of the cells (Housekeeping), as they carry old proteins to the cell's recycling bin (proteasome) and they help newly synthesized proteins fold properly. These activities are part of a cell's own repair system, called the "cellular stress response" or the "heat-shock response".

Some stress proteins have been recognized as molecular chaperones (Ellis and van der Vies, 1991; Gething*et al.*, 1993; Leppa and Sistonen, 1997; Kregel, 2002). Molecular chaperones help other polypeptides, to fold correctly while they are being synthesized in the ribosome, to direct proper re-folding after partial denaturation, and to transport other polypeptides to their final destination in the cell, which may include allowing them to pass through biological membranes. The molecular chaperones have the ability to bind reversibly to polypeptides, to facilitate or prevent their interaction with other polypeptides. They also act in the presentation of proteins to proteases for degradation. It is important to note that all molecular chaperones are not stress proteins and not all stress proteins are molecular chaperones (Kenny and Jepson, 2000). Cell proteins become venerable to denaturation and degradation, during times of stress and the protective role of HSPs as molecular chaperones, is thought to be one of their most important functions. HSP27 is a molecular chaperone, with an ability to interact with a large number of proteins to aid in the refolding of nonnative proteins

(Bryantsev*et al.*, 2007). It forms complexes with such proteins, thus preventing their non-specific aggregation and allowing them to be subsequently restored to their native structure in co-operation with ATP-dependent chaperones such as HSP70 (Beissinger and Buchner, 1998; Pandey *et al.*, 2000; Concannon*et al.*, 2003).

CONCLUSIONS

Characterization of candidate genes associated with thermos-tolerance in our livestock species suitable to agroclimatic conditions is the need of the hour, to combat the global food demand. Selection of suitable genotype /haplotype markers adapted to thermal stress, considering genotype-environment interactions (G × E) in addition to higher productivity should include in breeding programmes. Heat shock is one of the crucial hurdles to efficient livestock production. Defining the physiological mechanisms through which heat stress and other environmental factors influence complex, multifactorial traits, are critical for developing approaches to ameliorate current production issues and is a prerequisite for generating future strategies (genetic, managerial, nutritional, and pharmaceutical) to maximize livestock efficiency.

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