Heat Shock Proteins 12
Series Editors: Alexzander A. A. Asea · Stuart K. Calderwood

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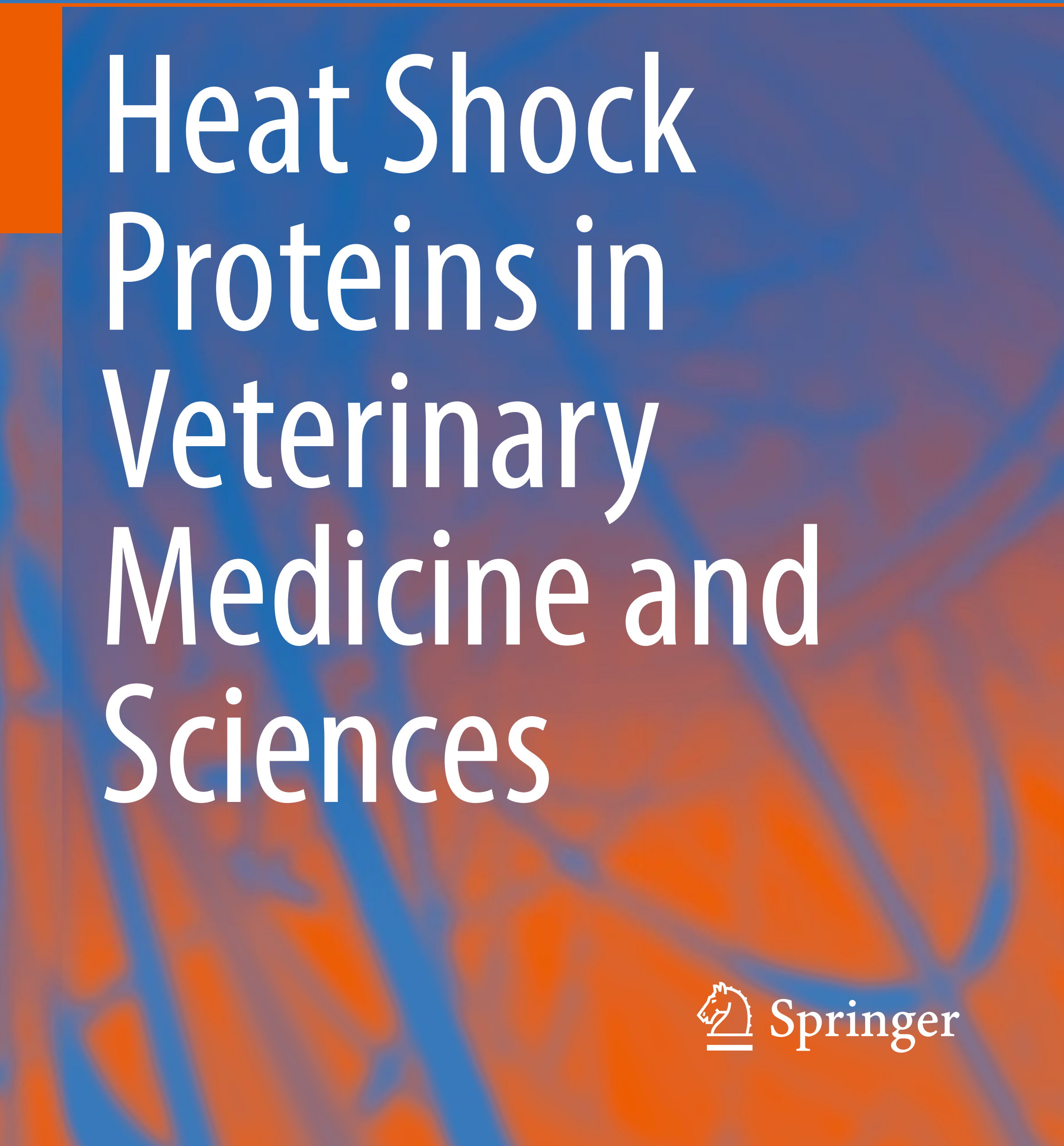

Heat Shock Proteins in Veterinary Medicine and Sciences

Springer

Heat Shock Proteins

Volume 12

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Heat Shock Proteins: key mediators of Health and Disease. Heat shock proteins (HSP) are essential molecules conserved through cellular evolution required for cells to survive the stresses encountered in the environment and in the tissues of the developing and aging organism. These proteins play the essential roles in stress of preventing the initiation of programmed cell death and repairing damage to the proteome permitting resumption of normal metabolism. Loss of the HSP is lethal either in the short-term in cases of acute stress or in the long-term when exposure to stress is chronic. Cells appear to walk a fine line in terms of HSP expression. If expression falls below a certain level, cells become sensitive to oxidative damage that influences aging and protein aggregation disease. If HSP levels rise above the normal range, inflammatory and oncogenic changes occur. It is becoming clear that HSP are emerging as remarkably versatile mediators of health and disease. The aim of this series of volumes is to examine how HSP regulation and expression become altered in pathological states and how this may be remedied by pharmacological and other interventions.

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Preface

Veterinary medicine is designed to advance our understanding and to promote innovative advances in basic and clinical veterinary sciences with the goal of improving the health and well-being of animals and, through them, the health, stability, and economic development of humans.

The book *Heat Shock Proteins in Veterinary Medicine and Sciences* provides the most comprehensive review on contemporary knowledge on the role of heat shock proteins (HSP) in veterinary medicine and sciences. Using an integrative approach to understanding heat shock protein physiology, the contributors provide a synopsis of novel mechanisms by which HSP is involved in the regulation of normal physiological and pathophysiological conditions.

To enhance the ease of reading and comprehension, this book has been subdivided into various sections: Section I reviews current progress on the role of HSP in relation to physiology and diseases in domestic animals, Section II evaluates the role of HSP as it relates to antioxidant and thermal stress responses in poultry, Section III focuses the reader on the role of heat shock proteins in aquatic animals, Section IV concentrates the reader's attention on the role of HSP in disease-causing parasites that plague animals.

Key basic and clinical research laboratories from major universities and veterinary hospitals around the world contribute chapters that review present research activity and importantly project the field into the future. The book is a must-read for veterinary doctors, researchers, postdoctoral fellows, and graduate students in the fields of veterinary medicine, animal physiology, animal husbandry, biotechnology, molecular medicine, microbiology, and pathology.

Toledo, Ohio, USA — Alexzander A. A. Asea
Houston, Texas, USA — Punit Kaur

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Editors Biography

Prof. Dr. Alexzander A. A. Asea is a highly innovative and accomplished world-renowned clinical and basic research scientist and visionary executive leader who has exceptional experience spearheading clinical and basic science research, training, education, and commercialization initiatives within top ranked academic biomedical institutes. Prof. Asea's initial findings studying the effects of Hsp72 on human monocytes lead to the proposal of a novel paradigm that Hsp72, previously known to be an intracellular molecular chaperones, can be found in the extracellular milieu where it has regulatory effects on immunocompetent cells – a term now called chaperokine. Prof. Asea has authored over 255 scientific publications including peer-reviewed articles, reviews, books, book chapters, editorials, and news headliners in a wide range of biomedical-related disciplines. Prof. Asea is the series editor of the widely successful book series *Heat Shock Proteins* (Springer Nature Publications) and is an editorial board member of 13 other scientific peer-reviewed journals. Currently, Prof. Asea is at the University of Toledo College of Medicine and Life Sciences in Toledo, USA.

Dr. Punit Kaur is an expert in onco-proteogenomics, with extensive training and experience in quantitative mass spectrometry imaging, protein chemistry, and biomarker discovery. Dr. Kaur's main research focus is on the use of heat-induced nanotechnology in combination with radiotherapy and chemotherapy in the cancer stem cell therapy. Dr. Kaur has published more than 40 scientific articles, book chapters, and reviews, and currently serves as editorial board member for the *European Journal of Cancer Prevention and the Journal of Proteomics and Bioinformatics*. Dr. Kaur is an editor of five books in the highly successful *Heat Shock Proteins* book series by Springer Nature Publishers. Currently, Dr. Kaur is a Visiting Scientist Professor at the University of Texas MD Anderson Cancer Center in Houston, USA.

Part I
Domestic Animals

Chapter 1
Thermotolerance in Domestic Ruminants: A HSP70 Perspective

**Iqbal Hyder, Manjari Pasumarti, Poonooru Ravikanth Reddy,
Chigurupati Srinivasa Prasad, Kamisetty Aswani Kumar,
and Veerasamy Sejian**

Abstract Thermal stress is one of the most important factors limiting ruminant production and thermotolerance studies in domestic ruminants has lot of bearing on the identification of prospective biomarkers for thermal stress, especially the heat stress. Heat stress in ruminants is characterized by heat shock response, which is mediated by different types of Heat Shock Proteins (HSP) like HSP60, 70, 90, 110, 27 among which some play a critical role in the initial stages of heat stress and some in the later stages. Among all HSP, HSP70 is considered as cellular thermometer and is indicator of quantum of stress experienced by the cell. At a given amount of stress the expression of HSP70 varies with species, breed, age and type of tissue indicating the variations in thermotolerance. Members of HSP70 family have many homologues like HSPA1A, HSPA1B, HSPA1L, HSPA2, HSPA4, HSPA5, HSPA6 & HSPA8 of which some are constitutive and some are inducible. These genes are elevated with heat stress in different type of cells at variable rate. The differences in thermotolerance among species and breeds are correlated with variations in different HSP70 family members. HSP70 can be viewed as prospective biomarker for marker assisted selection in animals in order to have more thermotolerant animals in future as a strategy towards Climate resilient ruminant production.

Keywords Adaptability · Heat Shock Proteins · HSP70 · Ruminants · Thermal stress · Thermotolerance

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Abbreviations

ACTH	Adrenocorticotropic hormone
ARD	Average relative deviation
CCI	Comprehensive climate index
CRH	*C*orticotropin releasing hormone
FAO	Food and Agriculture organization
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HPA	Hypothalamo-pituitary-adrenal
HSE	Heat shock element
HSF	Heat shock factor
HSP	Heat shock protein
IL	Interleukin
IPCC	Intergovernmental Panel on Climate Change
LCT	Lower critical temperature
MEC	Mammary epithelial cells
NO	Nitric oxide
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
RAD	Radia*tion*
RH	Relative humidity
RR	Respiration rate
RT	Rectal temperature
SNP	Single nucleotide polymorphism
TDI	Tuncia Dartos index
THI	Temperature humidity index
TI	Thermal index
TNF	Tumor necrosis factor
TNZ	Thermoneutral zone
UCT	Upper critical temperature
UTR	Untranslated region;
WS	Wind speed

1.1 Introduction

The animal agriculture has played a crucial role in the evolution of human civilizations, since domesticated species are renewable sources that provide humans with food and other tangible, intangible benefits. Especially the ruminants like cattle, sheep, goat and buffalo have always been a part and parcel of human habitations which is evident from various sources of human history. The ruminants over a period of time got adapted to thrive in different parts of the planet emerging as the most successful herbivores among mammals represented by 200 species among which there are 75 million wild and 3.5 billion domesticated animals across the globe (Hackman and Spain 2010) and some of them can survive in areas of feed/fodder shortage even up to less than half of their dietary requirement (Hyder et al. 2013). Today, livestock production is a dynamic and integral part of the food system, contributing 40% of the global value of agricultural output, 15% of total food energy, and 25% of dietary protein and supporting the livelihoods and food security of almost a billion people. The exploding population, globalization driven urbanization coupled with rising incomes during the last three decades have created a demanding situation on livestock products particularly in developing countries (FAO 2009). The World Bank estimates predicted that meat production should increase by 80% by 2030 that calls for efficient use of available animal resources. At the same time, the ruminant production is mired in several challenges with climatic factors like temperature, humidity, solar radiation etc. recognized as potential hazards in growth and production of livestock (Ganaie et al. 2013). Thermal stress seems to be exerting drastic effects on animal production that includes both heat and cold stress with the former being most important in major parts of ecosystems where ruminant domestication is prevalent. Heat stress forces a significant financial burden on livestock producers by decreasing production, reproductive efficiency and adversely affecting livestock health (Hyder et al. 2017). Increasing frequencies of heat stress are estimated to be more likely as a result of climate change and these will have adverse effects on livestock productivity (IPCC 2007). It is being predicted that these effects are going to be much more aggravated as there is a global consensus in the scientific community that climate change is already happening and that the further change is inevitable since by the year 2100 global temperatures may raise by 3.7–4.8 °C (IPCC 2014; Quere et al. 2014). Heat stress is a result of unfavorable negative balance between the net amount of energy flowing from the animal to its surrounding environment and the amount of heat energy produced by the animal (Hyder et al. 2017). Apart from the production aspects, in recent years, there is growing awareness regarding welfare of animals and heat stress is one of the major detrimental factors for animal welfare. The concern with the thermal comfort of livestock is justifiable not only for tropical countries that are characterized by high temperature and humidity, but also for temperate zone nations in which high ambient temperatures are becoming an issue (Nardone et al. 2010). It is expected that 20–30% of livestock will be at the risk of extinction (FAO 2007) due to changes in climate. There is evidence that climate change, especially elevated temperature has already changed the overall abundance, seasonality and spatial spread of farmed small ruminants (Van Dijk et al. 2010).

Hence, considering the multitude of effects due to thermal stress in animals, several adaptation measures have been recommended by the scientist across the globe and there is a consensus that it is generally faster to improve welfare, production and reproduction performances by altering the environment (Mader et al. 2006). But given the financial constraints of tropical farmers involved in ruminant production, intense environmental modifications like air conditioning, designer buildings etc. may be too expensive and economically unviable. This warrants for animals with improved thermotolerance that can also possess fair production and reproduction abilities so that an economic breakeven can be attained (Collier et al. 2005). Therefore, proper breed selection is a very valuable tool for sustaining animal production under an increasingly challenging environment.

The intended selection of thermotolerant animals/breeds will be successful if we have suitable biomarkers that can be used to select the animals and thereby breed them to establish heat resilient herds, one of the much sought aspects for climate resilient animal agriculture. Thermotolerance is a biological response which enables organisms to survive sub lethal high temperatures prior to experiencing a non-lethal heat exposure (Pawar et al. 2014). Several studies proved that Heat shock proteins (HSP) form a primary system for intracellular self-defense which are necessary for the cellular homeostasis especially important in a stressful environment. Among all the HSP, HSP70 is of particular interest since it is visualized as a rescue marker for cells that are vulnerable for stress induced cellular damage. With this background, the present chapter is targeted to enlighten the readers about the various aspects of thermotolerance in domestic ruminants from the purview of HSP70. Effort has been made to collect, arrange and synthesize information, deduce suitable and possible corollaries pertaining to alterations in HSP70 during various types of thermally induced stress conditions. For better comprehension of the heterogenous group of readers, the brief background about heat stress, indices to measure the heat stress, adaptation strategies of ruminants to heat stress are also presented in this chapter. Though thermal stress encompasses both heat and cold stress, majority of the chapter is emphasized on the former than latter since heat stress is more common and harmful for ruminant production due to spatial distribution of most of the domestic ruminants in the tropical areas with some salient aspects covered on the cold stress aspects too.

1.1.1 Thermal Stress as the Important Factor Influencing Livestock Production

Stress has been defined by various scientists taking into account multiple contexts. Some define it as a body reaction to stimuli that alters normal physiological equilibrium or homeostasis, often with detrimental effects (David et al. 1990) whereas some others view it as cumulative detrimental effect of a variety of factors on the health and performance of animals, or the magnitude of forces external to the body that tend to displace its systems from its basal state (Silanikove 2000a). Stress can also be defined as the inability of an animal to cope up with its environment that is reflected in failure of reaching genetic potential (Dobson and Smith 2000). In general, the homeothermic animals have a range of temperature where they do not have to expend energy in order to maintain their core body temperature, which means most of the energy can be diverted for production. This is called thermoneutral zone (TNZ) that is normally in the scale of 4 and 25 °C for most of the farm animals and the temperatures exceeding 25 °C will result in Heat stress (Mishra and Palai 2014; Dangi et al. 2015). When the ambient temperature on either side of the scale exceed the limits, it results in a condition where the energy reserves of the animal are diverted for maintenance of homeostasis at the cost of production, resulting in so called thermal stress. The thermal stress due to temperature going below the lower limit of the TNZ i.e., “lower critical temperature (LCT)”, is termed as cold stress and when it goes above the limit of TNZ i.e., the “upper critical temperature (UCT)” is termed as heat stress. Generally, the TNZ of an animal depends on age, species, breed, feed intake, diet composition, previous state of temperature, acclimation or acclimatization, production, specific housing and pen conditions, tissue insulation, external insulation, and behavior of an animal (Yousef 1985). For example, the TNZ of goats at 60–70% relative humidity, 5–8 km/h wind velocity and a medium level of solar radiation is 13–27 °C (Misra and Puneet 2009). In addition, genetic improvement programs aimed at enhancing production traits could well increase an animal’s susceptibility to high environmental temperatures due to the close relationship between metabolic heat generation and production level (Kadzere et al. 2002) making it as one of the important factors determining TNZ.

Heat Stress is described as the perceived discomfort and physiological strain associated with an exposure to an extreme and hot environment (Gupta et al. 2013). Though ambient temperature is considered as an important parameter to be regulated for optimal ruminant production, the animals actually experience what is called as “effective temperature” which is determined by other meteorological variables along with ambient air temperature. The most commonly used measure to assess this effective temperature especially at higher temperatures is Temperature Humidity Index (THI) (Thom 1959) and for colder climates, it is Wind Chill Index (Siple and Passel 1945). Apart from these two indices, others like Black Globe-Humidity Index (Buffington et al. 1981), Effective Temperature for dairy cows (Yamamoto 1983), Equivalent Temperature Index for dairy cows (Baeta et al. 1987), Thermal Comfort Index for sheep (Da Silva and Barbosa 1993), Heat Load Index for beef cattle (Gaughan et al. 2002), and Environmental Stress Index (Moran et al. 2001) also exist. As indices for heat and cold stress are separate, a comprehensive climate index (CCI) was proposed by Mader et al. (2010) which incorporates adjustments for Relative Humidity, Wind speed, and Radiation over conditions that encompass both cold and hot environmental conditions. In spite of THI being most widespread indicator of heat stress, its application is limited since it is an empirical representation that assumes all animals react similarly to environmental stressors, without accounting for other environmental effects (e.g., WS and RAD) and cow-specific effects (e.g., age and breed). New thermal indices (TI) that incorporated those environmental and physiological data in addition to cow specificities (e.g., breed and age) have been developed to overcome the various THI limitations (Gaughan et al. 2008; Mader et al. 2010). Several indices to measure heat tolerance have been developed over the years involving the biological factors. The THI was adjusted for wind and solar radiation based on changes in panting scores (Mader et al. 2006) and on a respiration rate index using dry bulb temperature, relative humidity (RH), wind speed (WS), and solar radiation (Eigenberg et al. 2005). Marai et al. (2007) suggests the use of average relative deviations (ARD) from normal (positive or negative) in