

*Review Article*

## **Impact of Heat Stress on Immune Responses of Livestock: A Review**

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### **ABSTRACT**

Climate change acts as a major threat to climate sensitive sectors such as agriculture and animal husbandry. This change in climate will be a greatest challenge to about 1.3 billion population who depends on animal husbandry as their livelihood. Heat stress is considered as one of the primary factors that imposes negative impacts on production and reproduction in farm animals. In addition, it also alters the immune functions of the animal and makes them susceptible to infectious diseases. Based on the duration of exposure, heat stress either enhances or suppresses the immune functions in farm animals. The stress signal acts mainly through hypothalamo-pituitary-adrenal (HPA) axis to modulate the immune response. Generally, it is considered that heat stress acts to shift the adaptive immune function from cell mediated to humoral immunity and thus weakens the animal immune function. Another aspect of this climatic change is the threat of emerging and re-emerging pathogens and disease vectors for which livestock needs fine-tuned immune system to fight against naïve pathogens. Thus, the heat stress-immune system interactions need to be studied thoroughly in order to introduce various management and nutritional strategies to alleviate the ill-effects of heat stress in farm animals.

*Keywords:* Climate change, Heat stress, Immunity,  
Livestock, HPA axis, Pathogens

### **ARTICLE INFO**

*Article history:*

Received: 6 November 2015

Accepted: 21 July 2016

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### **INTRODUCTION**

Livestock are called as the living bank for farmers. They contribute about 53 percent of world agricultural GDP (World Bank,

2009), and also to the economy by means of milk, meat, hide, eggs, drought power, manure etc. Apart from that, livestock also provide employment to 1.3 billion world population (FAO, 2009). The current world population of 7.3 billion is expected to reach 8.5 billion by 2030, 9.7 billion in 2050 and 11.2 billion in 2100 (UN, 2015) and about significant proportion of the population in developing countries will migrate to towns leading to increased urbanisation of 56.9% by 2025 (UNFPA, 2008). Ultimately, urbanisation will increase the standard of living of people, while the demand for high quality protein will also increase (Steinfeld et al., 2006). Henceforth, the concept of animal husbandry currently changes with major focus on food animal production. Animal protein is a cheap source of high quality protein with essential vitamins and micronutrients. Thus, to ensure nutritional security to the current growing population, animal protein seems to be inevitable. In order to provide quality animal meat to the consumers' fork, the farm animals should be healthy in terms of physiology, temperament and immunity.

However, there are various stressors, both biotic and abiotic, which challenge the animal's wellbeing. Temperature, solar radiation, photoperiod, humidity, geographical location, nutrition and socio-economic signals are the major abiotic stressors. Microbes such as bacteria, viruses, fungi and protozoa, as well as helminths and arthropod vectors, are the biotic stressors.

The term clinical disease is an outcome of the interaction of host factors, pathogen

potential and environmental influence. Even though host-pathogen interactions are essential for clinical disease development, the environment also plays an equally important role in modifying the host and pathogen factors (Kelley, 2004). Due to global warming, abrupt climatic conditions like storms, droughts, floods and extreme hot and cold temperatures are prevailing around the globe. With the changing climatic scenario, the frequency and duration of exposure of livestock to abiotic and biotic stressors increases. Current incidences of global climatic change lead to the evolution of new concepts in host-microbe relationship. High temperatures, accompanied by high relative humidity, favour the survival and multiplication of animal disease vector like ticks, fleas, tabanid flies, etc.; thus, the risk of spread of vector borne diseases also increases (Wittman & Baylis, 2000). The intercontinental spread of blue tongue virus by *Culicoides* spp. is a typical example (Rao et al., 2012). Furthermore, the increasing trend of international trade also favours the introduction of new disease species, which the host immune system has never been exposed. Introduction of bovine spongiform encephalopathy (BSE) through bovine offals (Pattison, 1998) and introduction of porcine respiratory and reproductive syndrome (PRRS) in swine in India are few examples of these.

Abiotic stressors such as heat and nutritional stress have a major impact on livestock productivity (Sejian et al., 2011). In the changing climate scenario, other factors like solar radiation, photoperiod

and humidity also synergises with the above stressors. Temperature influences the animals' productive and reproductive traits in a major way. In particular, heat stress is one of the crucial factors affecting livestock productivity (Rivington et al., 2009). Furthermore, the concept of global warming is alarming the planet earth day by day. According to the latest report released by IPCC (2013), there is an average of about 1.53°F (0.85°C) rise in global surface temperature from 1880-2012. Heat stress affects animal productive performances like milk yield, meat quality and reproductive performances like age at maturity, ovulation failure, embryo mortality, etc. (Shinde & Sejian, 2013). It also weakens the animal's immune system and makes them more prone to diseases. Although this has been observed by various researchers, the impact of heat stress on immune gene expression and process of heat stress mediating immune suppression at molecular level has not been dealt in detail in livestock. In order to withstand the existing and emerging pathogen challenges, the animal's immune system should be in a right tone. In order to mitigate immune suppression by means of various nutritional and hormonal interventions, an in depth understanding of the immunological pathways affected by heat stress and the mechanism by which it is affected is mandatory.

This review deals with the relationship between hypothalamo-pituitary-adrenal axis (HPA) and immune axis, the effects of heat stress on immunity, the mechanism by which heat stress affect immune response and

therefore, various nutritional interventions need to be taken to ameliorate heat stress mediated immune suppression.

## **STRESS AND IMMUNITY**

Various researchers defined stress as per their observations. It was Seyle in 1946, who gave the first definition about the animal response to stress. He called it as the 'general adaptation syndrome'. Stress is also defined as the biological response elicited when an animal perceives a threat to its homeostasis (Moberg & Mench, 2000). The threat is the stressor. An animal during its lifespan experiences non-threatening stress situations too which did not affect its health normally. Stress at its minimal level is always beneficial. A minimal level of stress called as good stress is required by all living organisms to perform a task. Stress is called as bad or stress will become a distress when it alters the normal biological functions like production and reproductive performances of an animal. Stress becomes important or needs attention in an animal lifetime in the point at which its welfare is compromised i.e. its survival, production and reproduction are affected. Thus, stress needs to be an important matter of discussion in livestock production because in a stressed animal, the energy balance and the body reserves will be mobilised to counteract or alleviate the stressor. This, in turn, leads to decreased production and reproductive performances. Furthermore, stress mediated interactions with the immune system suppresses its normal functions and leads the animal to a disease-prone state (Moberg & Mench,

2000). Therefore, the type of stresses that the animals encounter and its impact need to be studied and documented thoroughly to enhance better animal production in the changing climatic scenario. In general, animals encounter various stressors such as thermal stress, production stress, transportation stress, nutritional stress, immune stress, stress due to crowding, drought and environmental conditions (Kelley, 1980). In the arid and semi-arid tropical conditions, animals have to walk considerably long distances which in turn leads to walking stress (Sejian et al., 2012; Maurya et al., 2012). Currently, the concept of multiple stresses is evolving in animal stress physiology. Studies in Malpura sheep of northern India revealed that multiple stresses had significant influence on productive and reproductive parameters (Sejian et al., 2011). In the event of climatic change, stress due to adverse climatic conditions and emerging microbes and vector – borne diseases are some of which the animals have to encounter (Epstein et al., 1998).

Whenever an animal encounters a stressor, the central nervous system first begins to respond by sending signals to any of the biological systems viz. behavioural, autonomic nervous system, neuroendocrine system and immune system in order to alleviate or compensate the threat. It is not mandatory that all the four biological systems should respond together whenever a stress occurs. The response of each animal to a particular stress condition varies depending upon its previous exposure to

the stressors (Mason et al., 1991), genetic makeup (Marple et al., 1972), age (Blecha et al., 1983), season and physiological state. The neuroendocrine system responds mainly through the HPA by the release of glucocorticoids that are normally called as stress hormones (Webster & Glaser, 2008). They act to adapt the animal to cope up with the long-term stressors. The immune system responds to stress by enhancement or suppression of immune functions (Dhabhar, 2009). The immune system does not respond directly to stress but via neuroendocrine system. The stress related hormones act on the immune cell receptors to modulate the immune response.

## **IMMUNITY**

The immune system functions can be broadly classified into: (i) innate immunity and (ii) adaptive immunity. Innate immunity is the germ line encoded, non-specific, preliminary line of defence against the invading pathogens. The first entry of the pathogens is prevented at body's entry site through antimicrobial components in mucosa, sweat, tears, saliva, etc. In spite of this, if the pathogens enter, the specialised immune receptors called Pathogen Recognition Receptors (PRR) will identify the conserved molecular signatures called Pathogen Associated Molecular Patterns (PAMPs) present in the pathogens (Janeway & Medzhitov, 2002) and recruit leucocytes, particularly neutrophils, chemical mediators called pro-inflammatory cytokines, followed by macrophages. They ultimately kill the pathogens through reactive oxygen/

nitrogen species production and engulf them up in a process called phagocytosis (Bassett et al., 2003). Their processed fragments are presented to another phase of the immune system for specific immune response called adaptive immune system. Based on the pro-inflammatory cytokines that are released, the adaptive immune response may be either antibody mediated or cell mediated. All these mechanisms will ultimately lead to clearing of pathogens from the host body.

### **THE LINK BETWEEN STRESS AND THE IMMUNE SYSTEM**

Sympathetic innervation from brain connects the primary lymphoid organs and secondary lymphoid organs (Ader et al., 1995); thus, the catecholamine receptors in immune cells also contribute to immune cell activation by stress mechanisms. The end product of HPA axis activation results in glucocorticoid release, which has receptors in almost all organs including the immune cells (Ader et al., 2001).

### **THE STRESS AXIS**

It includes neural and endocrine organs and its secretory products and hormones released in response to stress. The HPA axis and sympathetic-adrenal-medullary system (SAM) are the crucial components that receive stress signals and act to relieve the stress mechanism or adopt the animal to the stressful condition (Riedemann et al., 2010). Figure 1 depicts the interaction between various endocrine axes with the immune system during stress.

### **SYMPATHETIC-ADRENAL-MEDULLARY SYSTEM (SAM)**

It is the sympathetic trunk of the autonomic nervous system (ANS) situated in the adrenal medulla. It acts by the release of epinephrine and nor epinephrine which are responsible for the characteristic flight or -fright mechanism. This helps the animals to overcome the stressor and it is the short term adaptation of the animal to acute stressor. These hormones act to enhance glycogenolysis causing increased glucose levels in circulation. The blood glucose will reach the stressed organ in order to meet the energy requirements and cope up with the stressor (Tort & Teles, 2011).

### **HYPOTHALAMO-PITUITARY-ADRENAL AXIS**

The core of stress response is believed to be based on the activation of HPA. The key components of this system include: (i) hypothalamus, and (ii) brain stem. The parvocellular neurons of CRH, arginine vasopressin (AVP) neurons of paraventricular nuclei of hypothalamus, CRH neurons of paraventricular and parabrachial nuclei of medulla and locus ceruleus innervate the system (Tort & Teles, 2011). They sense stressor and get activated to release CRH from paraventricular nucleus and arginine vasopressin from magnocellular neurons of hypothalamus. They act on chromaffin cells of anterior pituitary to release adrenocorticotrophic hormone (ACTH). ACTH, in turn, acts on adrenal cortex to stimulate synthesis and release of steroids leading to cholesterol

uptake. Cholesterol further gets converted into cortisol and corticosterone. Cortisol is the major glucocorticoid (GC) secreted in response to stress in mammals. GCs have receptors called glucocorticoid receptors (GRs) in almost all body tissues (de Kloet & Derijk, 2004). Glucocorticoid receptor exists as a complex in the cytoplasm of most cells including the immune cells. Binding of the hormone – receptor complex to Glucocorticoid Responsive Elements (GRE), located in the promoter region of the target gene, regulates the expression of target genes either positively or negatively. Basal levels of GCs are always present in circulation to meet the day-to-day metabolic activities. During acute stress, there is stimulation of HPA axis, followed by GC surge. It acts on vital systems to maintain homeostasis. When the stressor is removed, negative feedback mechanism acts to impair GC secretion, thus, the cycle goes on. In contrast, chronic stress has long-term increase in glucocorticoids in circulation which causes deleterious effects on the productive parameters and immunity. During chronic stress, the number of GC receptors in hippocampus gets reduced. As a result, the negative feedback mechanism which regulates the HPA axis is affected (Webster & Cidlowski, 1994). Another reason may be that the chronic stress activates the adrenal gland resulting in adrenal hypertrophy and henceforth results in increased and prolonged glucocorticoid secretion (Miller & Tyrrell, 1995).

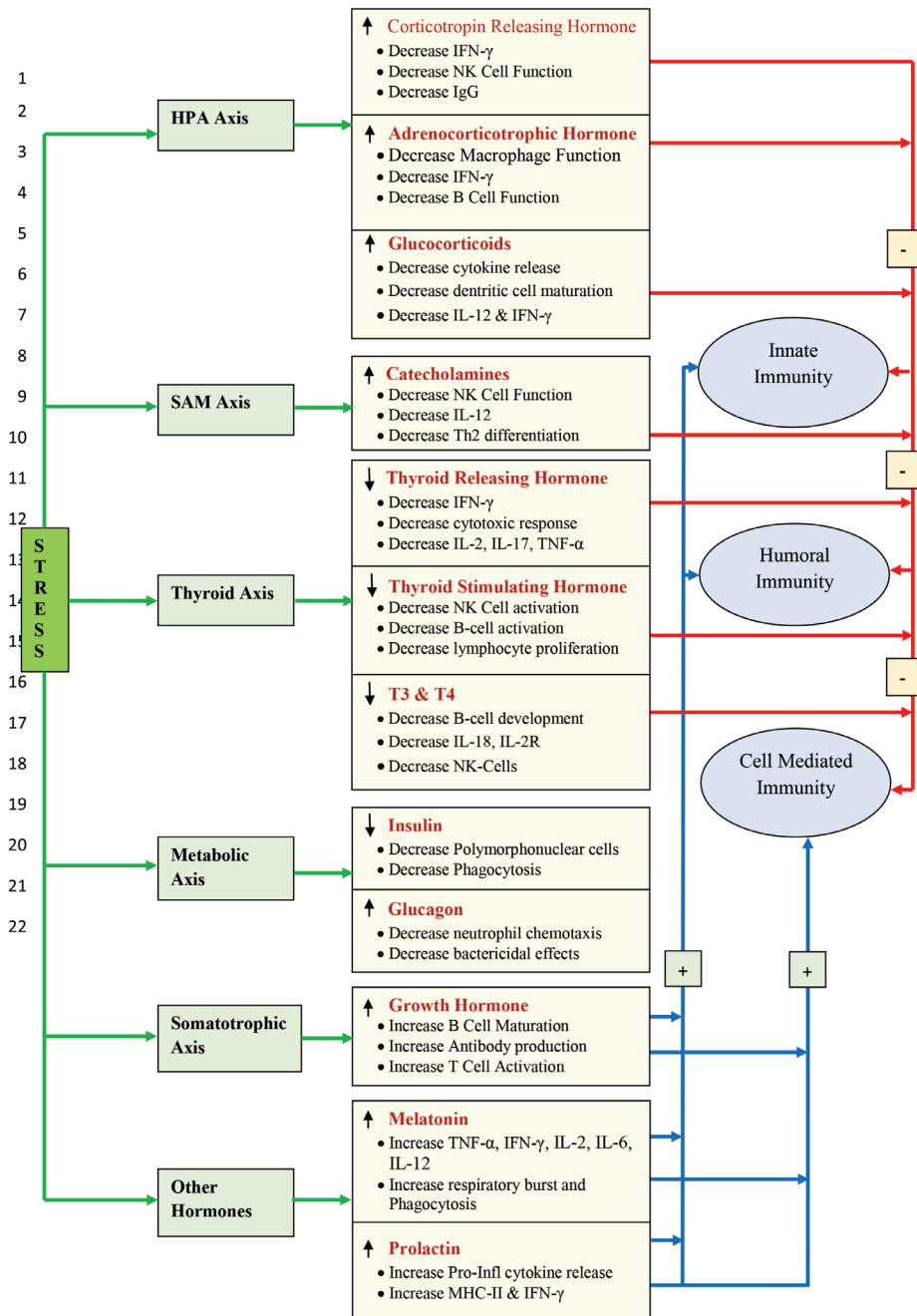
### **HEAT STRESS AS AN IMPORTANT FACTOR AFFECTING IMMUNITY IN LIVESTOCK**

The process of disease involves three factors; namely, host, pathogen and environment. Environment modulates the host and pathogen interactions in such a way that the pathogen overcomes the immune barrier of the host and establishes itself and henceforth, the outcome is the disease condition. In calf neonates, the first 18 hours of post natal life is very crucial as it determines the immune status of the animal. During this period, the intestinal epithelium is permeable to colostrum proteins, particularly immunoglobulins and thus passive transfer of immunity occurs from dam to offspring. Exposing dams and neonates to heat stress, however, has major impacts on the calf's immunity. Exposing heifers to high temperature during late pregnancy and early *postpartum* period not only reduces the concentrations of IgG, IgA, milk proteins and fatty acids in colostrums (Nardone et al., 1997) but also lowers the intestinal absorption of immunoglobulins (Stott et al., 1976). The low quality of Igs and reduced intestinal absorption in turn lead to calf mortality at high temperature (Martin et al., 1975).

### **HEAT STRESS AND DISEASE OCCURRENCE**

Heat stress directly or indirectly favours disease occurrence in animal host. Directly, high temperature favours the survival of organisms outside the host for a long time. This can be seen in the case of spores of





HPA-Hypothalamo-Pituitary-Adrenal; SAM-Sympathetic-Adrenal-Medullary; IFN-Interferon; IL- Interleukin; TNF-Tumor Necrosis Factor; IgG-Immunoglobulin G; T3- Tri-iodo-thyronine; T4-Thyroxine; MHC-Major Histocompatibility Complex; NK Cells- Natural Killer Cells; Th-T Helper Cell

Figure 1. The interaction between various endocrine axes with the immune system during stress

*Bacillus anthracis* and *Clostridium chauvoei* (Hall, 1988), which survive for a long period under high temperature and made available to infect the animals. Indirectly, chronic heat stress causes immune suppression in animals and makes them susceptible to diseases.

Moreover, global climatic change has created huge modifications on the macro and microclimate of both the host and the parasite and also altered certain trends of host-microbe interactions, namely: (i) shortened generation time of microbes which prefer high temperature leading to increased pathogen population and in turn increased risk of infection, and (ii) population of vectors like ticks, flies, midges, fleas normally requires high temperature, and hence they increase in number and their feeding frequency also increases. These lead to more chances for transmission of pathogen to animal host. The sub-tropical hot and humid conditions favour the tick population like *Boophilus microplus*, *Haemophysalis bispinosa* and *Hyalomma anatolicum* (Basu & Bandhopadyay, 2004). (iii) The extrinsic incubation period reduces due to high temperature has been seen in case of *Culicoides* (Wittman & Baylis, 2000). High ambient temperature combined with relative humidity predisposes dairy cows to clinical mastitis (Singh et al., 1996). The direct effect of heat compromises the udder immune system and also favours the housefly population (Sirohi & Michelowa, 2007).

## HEAT STRESS AND VACCINATION RESPONSE

Culling of diseased livestock is not economically feasible in developing countries of south Asia and Africa. Thus, regular vaccination seems to be a better option in order to protect the livestock from dreadful diseases like foot-and-mouth disease (FMD), anthrax, haemorrhagic septicaemia (HS), PPR, etc. The effects of heat stress on the immune response to vaccines have been reviewed based on the available literature. Varied results have been obtained by various researchers under different circumstances.

High temperature combined with high relative humidity failed to elicit humoral immune response to canine distemper vaccine and also failed to protect against the virus challenge. /however, the same temperature conditions did not affect the immune response to hepatitis vaccine (Webstar, 1975). The effect of chronic heat stress on FMD vaccination in mice model revealed that that chronic heat stress had adverse effect on cell mediated immune response than humoral immune response. Th1 based cell mediated immune responses like IgG<sub>a</sub> production, T cell multiplication, IFN gamma expression and antigen specific cytotoxic T lymphocyte activities were affected severely (Hu et al., 2007). The experimental study conducted by the same team also proved that both humoral and cell mediated immune responses to H5N1 avian influenza vaccine were affected by chronic heat stress. A new concept of up regulation



of CD4<sup>+</sup> CD25<sup>+</sup> Foxp3<sup>+</sup> T reg cells, with increased TGF- $\beta$ , IL-10, decreased Th1, Th2 cell responses, CD8<sup>+</sup> T cell proliferation and related cytokines was noticed in the study (Meng et al., 2013).

Various human studies revealed activation of latent viruses during stress conditions (McVoy & Adler, 1989). It was reported that glucocorticoids released during stress conditions activated the latent viruses by directly acting on the viral genome and also decreasing the immunological memory response (Glaser et al., 1995).

### **HEAT STRESS AND GUT HEALTH**

The gastrointestinal tract health is crucial in farm animals like cattle, sheep, goat, pigs, etc., as optimum production depends upon efficient feed conversion. The integrity of gastrointestinal tract is essential in order to maintain the normal homeostasis of gut microbiota. During heat stress, however, the blood flow to internal organs like intestine gets compromised and peripheral blood flow increases to dissipate the internal body heat (Lambert et al., 2002). The decreased blood flow leads to ischemia and necrosis of intestinal epithelial cells (Hall et al., 1999), decreases tight junctions between enterocytes which favour paracellular entry of bacterial pathogens. Increase in intracellular permeability helps in translocation of bacteria (Pearce et al., 2013) and its antigenic components, particularly LPS, thus leading to endotoxemia (Pearce et al., 2013). The toxin in turn affects the normal liver metabolism, leading to

steatohepatitis and decreased productive performance.

### **EFFECT OF HEAT STRESS ON IMMUNE RESPONSES**

Heat stress modulates various behavioural and physiological parameters in farm animals and in poultry species which have been discussed in detail by various reviewers (Lu, 1989; Kadzere et al., 2002; Marai et al., 2006; Yahav, 2009). Various authors recorded variable results indicating that heat stress as either an immune suppressing or immune enhancing factor in animal production. Stress affects both innate and adaptive immune response in animals.

### **HEAT STRESS AND INNATE IMMUNITY**

Heat stress reduces the relative weights of lymphoid organs like spleen, thymus and cloacal bursa (Aengwanich, 2008). The mechanical barriers, namely mucosa and skin, act as the first line of defense in innate immune response. Experiments in poultry revealed that exposure to heat stress caused mild acute lymphocytic enteritis (Quinteiro-Filho et al., 2010). Chronic heat stress could affect the integrity of respiratory tract and reduce pulmonary alveolar macrophages in lungs of mice, thus making the animals susceptible to Highly Pathogenic Avian Influenza or H5N1 (Jin et al., 2011).

NK cells are important components of the innate immune system present in systemic circulation and also in lymphoid organs like lymph nodes, spleen and bone marrow. They are involved in destruction

of tumour cells and infectious agents like bacteria, fungi and viruses. Studies in mice revealed that chronic heat stress in mice reduced the splenic NK cell cytotoxic functions. The inhibition may be due to increased glucocorticoid influence in the immune cell (Won & Lin, 1995).

The immune profile in PBMC of local Bama miniature pigs exposed to 21 days of heat stress revealed up regulation of the Toll Like Receptors (TLR) 2, 4 which are involved in identification of conserved molecules of microbes such as lipoprotein and lipopolysaccharides respectively (Ju et al., 2014). Heat stress also up regulated the TLR2, 4 genes in human monocytes (Zhou et al., 2005). Studies on the seasonal influences on TLR 1-10 mRNA expression in Black Bengal goats revealed that significant increases in TLR genes were noticed during summer season (Paul et al., 2015). The pro-inflammatory cytokines, namely IL-6, IFN- $\beta$ , which contributes to innate immune response were down regulated by heat stress (Jin et al., 2011).

#### **HEAT STRESS AND MUCOSAL IMMUNITY**

Heat stress reduces the blood flow to intestine, lowers the integrity of intestinal epithelium, causes villi desquamation and reduces the villi height and crypt depth (Yu et al., 2010; Yu et al., 2013). Furthermore, the innate immune components like mucosal barrier, toll like receptors, secretory Ig A, intestinal intraepithelial lymphocytes production (Deng et al., 2012), expression

of cytokines responsible for humoral and cell mediated immune response were down regulated in intestine by heat stress. Reduction of intestinal immune function enabled bacterial translocation to mesenteric lymph node (Liu et al., 2012).

#### **HEAT STRESS AND ADAPTIVE IMMUNITY**

Adaptive immune response collectively represents the humoral and cell mediated immune response. Experimental results in farm animals and poultry revealed variable adaptive immune responses during heat stress. Table 1 represents the adaptive immune responses elicited by livestock during heat stress conditions.

#### **MECHANISM OF HEAT STRESS IMPACTING LIVESTOCK IMMUNE SYSTEMS**

Various stressors including heat stress induce the endocrine system to increase catecholamines and glucocorticoids. These hormones modulate the cytokine release and thereby regulate immune responses.

#### **GLUCOCORTICOIDS MEDIATED LYMPHOLYSIS**

Experiments in poultry revealed that decrease in relative weights of immune organs like spleen, cloacal bursa and thymus. This might be due to glucocorticoid induced lympholysis and redistribution of lymphocytes from systemic circulation to other organs (Jain, 1993).

### MECHANISM OF INHIBITION OF INNATE IMMUNITY

Stress induced glucocorticoids act to inhibit the pro-inflammatory cytokines, namely TNF- $\alpha$ , IL-6, IL-8, which are required to initiate an innate immune response through inhibition of p38 MAPK pathway which helps in maintaining their stability (Abraham et al., 2006). GCs also enhance IL-10, an anti-inflammatory cytokine which is normally found at the end of immune response (Marchant et al., 1994). The cytotoxic function of NK cells are inhibited by catecholamines which act through adrenergic receptors to elevate cAMP levels that will in turn decrease the cytotoxic functions (Whalen & Bankhurst, 1990). The hyperthermia mediated suppression of NK cell activity is due to the inhibition of perforin and granzyme enzymes (Koga et al., 2005). GCs upregulates innate immune system via stimulation of Pattern

Recognition Receptors TLR2, TLR4 (Galon et al., 2002).

### MECHANISM OF INHIBITION OF ADAPTIVE IMMUNITY

Th1 cells are involved in cell mediated immune response whereas Th2 cells are responsible for humoral immune response. The modulation of cytokine gene expression in fact alters the immune function from Th1 to Th2 and vice versa. Th1 cells secrete IFN- $\gamma$ , IL 2, TNF  $\beta$  which contributes to cellular immunity. Th2 cells secrete IL-4, IL-10 and IL-13, which contribute to humoral immunity. IL-12, in combination with IFN-gamma, converts uncommitted T helper (Th0) cells to Th1 cells, whereas cytokines IL-4 and IL-10 induce Th2 cell production. Both Th1 and Th2 cell mediated are inhibitory to each other (Elenkov & Chrousos, 1999). Glucocorticoids acts to inhibit the release of IL-12 and IFN  $\gamma$  which

Table 1  
*Effects of heat stress on adaptive immune responses of livestock*

| Animal  | Immune Parameters studied                       | Effect of heat stress on the immune parameter | References                                      |
|---------|---|---|---|
| Poultry | Humoral immunity                                | Unaltered                                     | Regnier et al. (1980)                           |
| Calves  | Mitogen stimulation index                       | Unaltered                                     | Kelley et al. (1982a)                           |
| Pigs    | Mitogen stimulation index & antibody production | Unaltered                                     | Bonnette et al. (1990)                          |
| Poultry | Antibody response                               | Unaltered                                     | Donker et al. (1990)                            |
| Poultry | Antibody mediated primary immune response       | Decreased                                     | Thaxton et al., (1968); Subbarao & Glick (1970) |
| Poultry | Humoral immunity                                | Decreased                                     | Mashaly et al. (2004)                           |
| Cattle  | Cell mediated immunity                          | Unaltered                                     | Lacetra et al. (2002)                           |
| Calves  | Cell mediated immunity                          | Decreased                                     | Kelley et al. (1982b)                           |
| Cattle  | B and T- cell mitogen response                  | Decreased                                     | Elvinger et al.(1991)                           |

are the major cytokines involved in Th1 based cell mediated immunity (Elenkov et al., 1996). Furthermore, the expression of IL-12 receptors in NK cells and Th1 cells are down regulated by glucocorticoids (Wu et al., 1998), and thus the immune function get shifted from Th1 to Th2.

Dendritic cells are potent APCs and link the innate and adaptive immune response as they are involved in phagocytosis and antigen presentation. They also express more MHC Class II and co-stimulatory molecules like CD80, CD83 and CD86 on their cell surface. GCs act to inhibit expression of these molecules on DCs and thereby prevent its maturation (Girndt et al., 1998). In addition, catecholamines, which include adrenaline and noradrenaline, are also released during stress conditions to inhibit the production of IL-12, development of Th1 cells and Th2 differentiation (Elenkov et al., 1996). Treatment with adrenergic agonist revealed inhibition in IFN  $\gamma$  production by Th1 cells (Sanders et al., 1997).

### MOLECULAR RESPONSES TO HEAT STRESS

Stress leads to activation of hypothalamic-pituitary adrenal axis and ultimately the release of glucocorticoids. Glucocorticoids, in normal pulsatile release, enhances the pro-inflammatory cytokine release. However, chronic rise in glucocorticoid levels is inhibitory to majority of immune cytokines. Glucocorticoid acts in various ways to inhibit cytokine release. Table 2 represents various genomic and non-genomic mechanisms by which GCs suppress cytokine release.

### GENES ASSOCIATED WITH IMMUNE FUNCTIONS DURING HEAT STRESS

The stress related immune responses in poultry species revealed that acute stress is beneficial to the bird as it the immune system. On the other hand, chronic stress shifts the T helper cell response to T regulatory cell and also TGF- $\beta$ , a regulatory cytokine production, thereby it suppresses immune response (Shini et al., 2010). Meng et al. (2013) who demonstrated that chronic heat could suppress both Th1 and Th2 lymphocyte based immune response for H5N1 avian influenza virus through upregulation of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg cells, immune cytokine TGF- $\beta$  gene expression. The heat stress signaling pathway was observed to be distinct from endotoxemic pathway in mice. It acts through HSFs such as HSP 70 and Stress Activated Protein Kinase pathways resulting in an early increase in the expression of *hsp72*, *c-fos* and *c-jun* genes. This in turn leads to the expression of a peculiar cytokine pattern consisting of increased IL-6 and IL-10 expression and decreased TNF- $\alpha$ , IL-1 $\beta$  expression. The pattern recognition receptor, namely *TLR-4*, is highly expressed whereas there was no significant difference in *TLR-2* gene expression (Welc et al., 2013). The endotoxemic pathways differ from the earlier in which increased expression of *IL-1 $\beta$* , *IL-6*, *TNF- $\alpha$*  genes are evident (Lang et al., 2003). Chronic heat stress could influence complement system, a component of the innate immune system in the intestine of rats (Lu et al., 2011). Furthermore, the

chemokine signalling pathways and HSP expression were reported to be down regulated during heat stress (Liu et al., 2014). This might be due to the inhibition of JAK-STAT signalling pathways, which play an important role in induction of immune cells to release cytokines and chemokines. The JAK-STAT proteins are thermolabile in nature and get decreased during heat stress (Nespital & Strous, 2012). Moreover, differential expression of adaptive immunity genes were noticed viz. up regulation of HSP-70 genes and down regulation of RT1-Bb genes, which encode for beta chain of MHC-class II. Both the genes are involved in antigen presentation to CD4<sup>+</sup> T cells and ultimately the CD4<sup>+</sup> T cell stimulation gets affected (Liu et al., 2012). Also, heat stress reduced the expression of MHC class II and co-stimulatory molecules like CD40, CD80 and CD86 by antigen presenting cells, thus delayed DC maturation (Jin et al., 2011). The cytokine genes for both Th1 (IL-2, IFN- $\gamma$ ) and Th2 (IL-4, IL-10) cell responses were down regulated during heat stress (Liu et al., 2012). Heat stress experiments in Bama miniature pigs revealed that IL-12,

the key cytokine gene to initiate cellular immune response was upregulated but IL-2 and IFN- $\gamma$ , which are also involved in CMI process were down regulated, revealing differential expression of immune cytokine genes (Ju et al., 2014). Acute heat stress exposure in cattle led to up regulation of IL-17, a cytokine associated with innate immune response up to 48 hrs after heat stress. Moreover, the genes involved in humoral immune response (Cd83, HSPA1A & IL1A) showed increased expression during heat stress (Mehla et al., 2014). Table 3 describes the different immune response genes getting expressed during heat stress condition in animals.

#### **SIGNIFICANCE OF OPTIMUM NUTRITION FOR IMMUNE FUNCTION UNDER HEAT STRESS**

The various strategies need to be adopted for management of animals during heat stress include shelter management, evaporative cooling systems such as misting, fogging, pad cooling, sprinkling or dripping, modified nutrition strategy and genetic selection of animals for heat tolerant genes.

Table 2  
*Different mechanisms by which glucocorticoids suppresses cytokine function*

| General mechanisms involved                                       | Cytokines affected     | References               |
|---|------------------------|--------------------------|
| Suppression of cytokine gene transcription                        | IL-1, IL-2, IL-3, IL-8 | Smoak & Cidlowski (2007) |
| Decrease in cytokine secretion                                    | IL-1                   |                          |
| Destabilization of cytokine mRNAs                                 | IL-1, TNF, GM-CSF      |                          |
| Inactivation of the released cytokine by inducing decoy receptors | IL-1                   |                          |

TABLE 3  
Different immune regulatory genes expressed and their functions during heat stress

| Species | Immune genes       | Function   | Up regulation/<br>Down regulation | References             |
|---------|--------------------|--|-----------------------------------|------------------------|
| Mice    | IL-6               | Pro-inflammatory cytokine                            | Up regulated                      | Welc et al.<br>(2013)  |
|         | IL-10              | Anti-inflammatory, Immune regulatory cytokine        |                                   |                        |
|         | TLR-4              | PRR for LPS  | Down regulated                    |                        |
|         | TNF- $\alpha$      | Acute inflammatory response                          |                                   |                        |
|         | IL-1 $\beta$       | Pro-inflammatory cytokine                            |                                   |                        |
| Cattle  | IL-17A             | Innate immunity                                      | Up regulated                      | Mehla et al.<br>(2014) |
|         | HSPA1A             | Induce antibody production & T cell activation       |                                   |                        |
|         | Cd83               | Antigen presentation to B lymphocytes                | Suppressed earlier; induced later |                        |
|         | IL1A               | T cell dependant antibody production                 |                                   |                        |
|         | CXCL5              | Chemo attractant for neutrophils                     |                                   |                        |
|         | F $\gamma$ R1A     | Antigen presentation via MHC class I                 |                                   |                        |
| Poultry | IL-1 $\beta$       | Pro-inflammatory cytokine                            | Increased during acute stress;    | Shini et al.<br>(2010) |
|         | IL-6               | Pro-inflammatory cytokine                            |                                   |                        |
|         | IL-18              | Pro-inflammatory cytokine; involved in CMI           |                                   |                        |
|         | TGF $\beta$        | Immunoregulatory cytokine                            | Increased during chronic stress   |                        |
|         | CCL16              | Chemo attractant for lymphocytes                     |                                   |                        |
| Pigs    | TLR2, TLR4         | Innate immune response                               | Up regulated                      | Ju et al.<br>(2014)    |
|         | IL-12              | Induction of Th1 based cell mediated immune response | Up regulated                      |                        |
|         | IFN $\gamma$       |  | Down regulated                    |                        |
| Rats    | IL-2, IFN $\gamma$ | Th1 based cell mediated immune response              | Down regulated                    |                        |
|         | IL-4, IL-10        | Th2 based humoral immune response                    |                                   |                        |



cont'd Table 3

|      |   |   |                |                       |
|------|---|---|----------------|-----------------------|
| Rats | HSPA1A,<br>ZBTB16,<br>CSF2, HPX,<br>IL22RA2,<br>PTDSR,<br>LOC301133,<br>BCL6,<br>MAdCAM1,<br>PPARA,<br>CDK6,<br>VEGFA |   | Up regulated   | Liu et al.<br>(2014)  |
|      | TNFSF6,<br>MS4A2,<br>CCL5, SPN,<br>CCR5,<br>MM9, IR4,<br>TLR2, CCL4,<br>S100A9, RT2-<br>Bb                            | Cytokine-cyokine interaction              | Down regulated |                       |
| Rat  | RGD1561028,<br>HSP90AA1,<br>HSP90AB1,<br>HSPA11, and<br>HSPA8   |   | Up regulated   | Lu et al.<br>(2011)   |
|      | RT1-Bb,<br>CCL5,<br>CCR5,<br>CXCR3 and<br>Fas   | Cytokine-cytokine receptor<br>interaction | Down regulated |                       |
|      | IL22RA2<br>CSF2<br>TNFSF14  |   | Up regulated   |                       |
|      | Cd55, F3  | Complement & coagulation<br>cascades      | Down regulated |                       |
|      | Fgb,<br>Serpine1, and<br>Serpine 2  |   | Up regulated   |                       |
| Mice | IL-10, TGF-b  | Immunoregulatory cytokines                | Up regulated   | Meng et al.<br>(2013) |
| Mice | MHC-II,<br>CD40, CD80,<br>and CD86  | Co-stimulatory molecules                  | Down regulated | Jin et al.<br>(2011)  |
|      | IL-6 and<br>IFN- $\beta$  | Pro-inflammatory cytokine                 |                |                       |
|      | IL-10   | Immunoregulatory cytokine                 | Up regulated   |                       |

The nutrients which enhance immune response in heat stressed animals include vitamins, minerals, antioxidants, prebiotics, probiotics, synbiotics, etc.

## VITAMINS

Vitamin A acts to maintain the normal mucosal and epithelial barrier, thereby helps to strengthen the mechanical barriers which are the components of innate immune response (Sordillo et al., 1997). Thus, it is required for maintaining udder health in milch animals. Moreover, supplementation of vitamin A augments the functions of anti-oxidant enzymes like glutathione peroxidase, superoxide dismutase, etc. (Jin et al., 2014). The supplementation of vitamin A also results in increased pro-inflammatory cytokines like IL-1, TNF- $\alpha$ , Ig M, Ig G and Ig A, soluble CD4, CD4/CD8 ratio, decreased CD8 (Jin et al., 2014) and aids in immunoglobulin transport proteins production (Tjoelker et al., 1990). Selenium, a trace element, plays an important role in immune function in combination with vitamin E. The anti-oxidant enzyme, glutathione peroxidase incorporates selenium within it, thus it is indirectly involved in protection of the body from oxidative stress. Moreover, selenium supplementation in diet decreased the incidence of clinical mastitis and somatic cell count (Smith et al., 1997). Selenium – vitamin E supplementation positively influences chemotaxis (Aziz & Klesius, 1986), phagocytic ability (Grasso et al., 1990) and oxidizing property of neutrophils (Aziz & Klesius, 1986).

## TRACE MINERALS

Copper is essential for the development of immune organs and antibody production (Lukasewycz & Prohaska, 1990). Copper-deficiency was reported to reduce the phagocytic ability of neutrophils and macrophages (Babu & Failla, 1990a; Babu & Failla, 1990b), IL-2 production and thus lymphocyte proliferation (Bala & Failla, 1992). Keratin acts as a mechanical barrier in organs such as mammary gland and in appendages such as horn, hoof, etc. Zinc is involved in various stages of keratinization (Paulrud, 2005). Providing zinc supplementation in organic form during summer helps in maintaining udder health by strengthening keratin layer and preventing mastitis (Popovic, 2004). Meanwhile, iron helps in the development of immune organs like thymus, spleen, lymph node and cloacal bursa. Experiments with iron-glycine supplementation revealed iron particularly influences thymus development in animals (Feng et al., 2007) and birds (Sun et al., 2015). Chromium supplementation helps in the development of primary immune response with increased Ig M and Ig G concentration (Moonsie-Shageer & Mowat, 1993).

## PROBIOTICS

Probiotics are mixture of live micro-organisms which are beneficial to animal's health when given in adequate amounts. These live organisms occupy the entire length of the gut to protect against pathogens entry and colonisation by a process called "competitive exclusion" or "bacterial

antagonism” or “bacterial interference” (Lloyd et al., 1977) and strengthen the intestinal mechanical barrier. Furthermore, probiotics compete with pathogenic bacteria for nutrition and attachment site. They also produce antimicrobial peptides such as colicins and bacteriocins (Lee et al., 2008) and stimulate cytokine production (Marin et al., 1997).

### PREBIOTICS

Prebiotics are said to be undigestible feed ingredients that beneficially affect the host by selectively stimulating the growth or activity of limited number of bacteria in colon (Gibson & Roberfroid, 1995). Feeding of fructose-oligosaccharide and mannon oligosaccharide increased antibody responses (White et al., 2002).

### SYNBIOTICS

Synbiotics, a combination of probiotics and prebiotics, is supplemented in farm animals. The necessity for the combination is that prebiotics acts as nutritional substrate for probiotic organisms, thus helps in improving or maintaining the gut health. Synbiotics acts as a stimulant for phagocytosis and releases cytokines like TNF-alpha, IFN-gamma and antibody production (Kabir et al., 2004). Synbiotics are reported to increase the antibody response to vaccines (Hassanpour et al., 2013).

### CONCLUSION

In the global climate change scenario, heat stress is the predominant stress affecting

livestock production through emergence of different vector borne diseases. This review has thrown light that in addition to altering the productive and reproductive performance, heat stress can also alter the immune functions of animals to bring down their production. The stress hormones – cytokine interactions are responsible for altered immune functions during heat stress. In particular, the highly specific adaptive immune mechanisms are affected by heat stress. In more specific, heat stress deteriorates the cell mediated immune responses. The role of heat stress during critical events in an animal like passive transfer of maternal antibodies, vaccination and new pathogen challenge has been widely discussed. This reveals that heat stress needs to be considered as an important factor compromising animals’ health. Furthermore, various managerial and nutritional interventions were discussed in detail during such instances to prevent the harmful impacts of heat stress on animal’s welfare. This literature review can serve as a good reference material for researchers who aim at improving livestock production in the changing climate scenario by optimising the immune system functioning in livestock.

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