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Mayank Patel
Ph.D. Scholar, Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Anamika Pandey
Ph.D. Scholar, Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Shamshad Ali
Ph.D. Scholar, Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Preeti Verma
Ph.D. Scholar, Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Prem Kumar
M. V. Sc. Scholar, Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Vikrant Singh Chouhan
Senior Scientist, Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Corresponding Author:
Mayank Patel
Ph.D. Scholar, Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Effect of heat stress on innate and acquired immunity of livestock

Mayank Patel, Anamika Pandey, Shamshad Ali, Preeti Verma, Prem Kumar and Vikrant Singh Chouhan

Abstract
Heat stress poses a significant challenge in global livestock production systems, primarily due to increasing global temperatures linked to climate change. High ambient temperatures and humidity levels can adversely affect the health and productivity of livestock animals. In addition, it also compromises their immune system and makes them more susceptible to diseases. The duration of exposure to heat stress can either enhance or suppress immune functions in farm animals. This stress signal operates through the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis, influencing the immune response. The first line of defence against pathogens, known as innate immunity, is essential for immediate responses to infections. Heat stress has been observed to impair various components of the innate immune system in livestock animals. It can compromise the integrity of the skin and mucosal barriers, as well as reduce the proliferation of immune cells. Generally, it's believed that heat stress shifts the adaptive immune function from cell-mediated to humoral immunity, weakening the animals' immune responses. Understanding the immunological effects of heat stress is crucial for livestock producers and researchers to implement effective management strategies, ensuring the health and welfare of animals in the face of mounting climate challenges.

Keywords: Heat stress, innate immunity, acquired immunity

Introduction
In the upcoming years, dealing with heat stress will pose a significant challenge due to the rising global temperatures and the associated decline in available agricultural land, alongside a growing human population. This situation is causing considerable concern for both farmers and the livestock industry (Renaudeau *et al.*, 2012) [1]. Extreme temperature can cause stress in animals, resulting in changes in their pulse rate, respiration rate, body temperature, milk composition (Patel *et al.*, 2022) [2] and metabolism, ultimately affecting their growth, productivity and immune system. As a response to heat stress, animals often seek relief by moving closer to water bodies or seeking shade. Thermoregulation helps the animal to maintain their body temperature in a balanced state. Metabolism plays a crucial role in generating heat for various body functions. However, the combination of increased metabolic heat production and rising environmental temperatures can hinder the effective dissipation of excess heat, contributing to heat stress. Furthermore, heat stress can have a detrimental impact on the animals' immune systems, making them more vulnerable to illness and increasing morbidity and mortality rates. The key to the survival of livestock lies in their ability to adapt and maintain a robust immune system.

The brain detects heat stress conditions and triggers two important hormonal pathways: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis. The activated hypothalamus releases corticotropin-releasing hormone (CRH), which signals the pituitary gland to produce adrenocorticotropin hormone (ACTH). ACTH, in turn, prompts the adrenal gland to produce glucocorticoids, noradrenaline and adrenaline (catecholamines). The primary glucocorticoid involved is cortisol. Glucocorticoids play a vital role in mitigating the body's response to heat stress and have anti-inflammatory effects on the immune system, while catecholamines have pro-inflammatory effects.

Effect of heat stress on innate immunity
1. Effect of heat stress on anatomical barriers
Anatomical barriers in the body encompass physical barriers, represented by the skin and mucous membranes, as well as chemical barriers, such as the presence of hydrochloric acid in

the stomach and enzymes in tears and saliva. Maintaining the health of the gastrointestinal tract is of paramount importance in farm animals to ensure optimal production. The integrity of the gastrointestinal tract is vital for preserving the normal balance of gut microbiota. However, during episodes of heat stress, blood flow to internal organs like the intestine is compromised, and peripheral blood flow increases to dissipate internal body heat (Lambert *et al.*, 2002) [3]. Reduced blood flow can lead to ischemia and necrosis of the intestinal epithelial cells (Hall *et al.*, 1999) [4], causing a decrease in tight junctions between enterocytes, which makes it easier for bacterial pathogens to enter the body through the gaps. This increased permeability facilitates the translocation of bacteria and their antigenic components, especially lipopolysaccharides (LPS), leading to endotoxemia (Pearce *et al.*, 2013) [5]. These toxins, in turn, affect normal liver metabolism, resulting in steatohepatitis and reduced productivity. Heat stress can lead to oxidative stress, which in turn affects the structure and function of the intestine. Heat stress significantly reduces villus height, crypt depth, villus height to crypt depth ratio, and mucosal surface, and increases the shedding of villi. Additionally, the protective role of the intestine is compromised as heat stress affects the expression of tight junction proteins, disrupting their barrier function and potentially leading to endotoxemia.

As a response to heat stress, pigs increase peripheral blood flow to dissipate heat, which reduces blood flow to internal organs, including the gastrointestinal tract (GIT) (Collin *et al.*, 2001) [6]. This decreased blood flow results in reduced oxygen and nutrient supply to the GIT, leading to a break in intestinal barrier integrity (Hinnebusch *et al.*, 2002) [7]. The intestinal barrier is a critical component of the GIT, consisting of a single layer of enterocytes and intercellular tight junctions (Yan *et al.*, 2006) [8]. It acts as a selective, permeable membrane responsible for nutrient absorption and defending against harmful substances (Turner *et al.*, 2009) [9]. Heat stress disrupts these tight junctions, increasing the circulation of endotoxins and potentially causing increased intestinal permeability, raising the risk of endotoxemia (Pearce *et al.*, 2013) [5]. The single layer of intestinal epithelial cells (IECs) held together by tight junctions, which include transmembrane proteins like occludin, claudins, and junctional adhesion molecules, forms the intestinal epithelium (IE) (Suzuki, 2020) [10]. This unique structure is designed to prevent harmful microorganisms, antigens, and toxins from entering the bloodstream from the gut lumen (Williams *et al.*, 2014) [11]. Additionally, IECs play a role in influencing immune cell recruitment and activation through the production of cytokines and chemokines (Oswald, 2006) [12], making them a crucial component of innate immunity.

2. Effect of heat stress on phagocytic cells

Leukocytes are the primary components of the immune system, responsible for defending the body against invading infectious agents such as bacteria, viruses, fungi and parasites. Heat stress in dairy cattle has a significant impact on the population of leukocytes. An indicator of thermal stress in animals is the neutrophil to lymphocyte ratio, which generally increases in stressful conditions (Stanger *et al.*, 2005) [13]. Glucocorticoids, a type of steroid hormone, contribute to the elevated neutrophil to lymphocyte ratio by promoting the release of neutrophils from the bone marrow into the bloodstream and inhibiting their migration from the bloodstream to other body compartments. Parmar *et al.* 2013 [14] and Lynch *et al.* 2010 [15] reported higher neutrophil to lymphocyte ratios as stress indicators during heat stress. Dayal *et al*. 2017 [16] also found an increase in the percentage of neutrophils during stressful conditions.

3. Effect of heat stress on cytokines

Cytokines represent a diverse category of small proteins, typically ranging from about 5 to 25 kilodaltons (kDa), and play a crucial role in cell signalling. These signalling molecules are generated by a wide variety of cells, including macrophages, T lymphocytes, B lymphocytes, endothelial cells, fibroblasts, mast cells and various stromal cells. Cytokines have been categorized into different groups such as lymphokines, chemokines and interleukins, based on their assumed functions, the cells that secrete them, or the specific actions they target.

Classification of important cytokines

Sr. No	Category	Inflammatory action	Sub-types
1.	Interleukins	Pro-Inflammatory	IL-1α, IL-1β, IL-6, IL-8
		Anti-Inflammatory	IL-4,IL-10,IL-13
2.	Tumor Necrosis Factors	Pro-Inflammatory	TNF-α
3.	Interferons	Pro-Inflammatory	INF-α, INF-β
		Anti-Inflammatory	INF-γ
4.	Colony Stimulating Factors	Stimulating growth & differentiation of immune cells	Types 1-4

Experiments involving heat stress in Bama miniature pigs have shown that the key cytokine gene IL-12, which initiates the cellular immune response, was upregulated during stressful conditions. However, the genes for IL-2 and IFN-γ, which are also involved in the process of cell-mediated immunity, were downregulated (Ju *et al.*, 2014) [17]. In cattle exposed to acute heat stress, there was an upregulation of IL-17, a cytokine associated with the innate immune response, for up to 48 hours following the heat stress. In contrast, Pearce *et al*. 2013 [5] reported the downregulation of IL-8 in pigs during heat stress.

Stress-induced glucocorticoids have the effect of inhibiting pro-inflammatory cytokines, specifically TNF-α, IL-6, and IL-8, which are necessary for initiating an innate immune response. This inhibition occurs through the suppression of the p38 MAPK pathway, which plays a role in maintaining the stability of these cytokines, as noted by Abraham *et al.* 2006 [18]. Additionally, glucocorticoids enhance the production of IL-10, an anti-inflammatory cytokine that is typically found at the end of the immune response, as discussed by Marchant *et al.* 1994 [19].

4. Effect of heat stress on Toll-like receptors (TLRs)

Toll-like receptors (TLRs) are a class of proteins that play a crucial role in the innate immune system. These receptors are typically found on the membranes of various types of leukocytes, including dendritic cells, natural killer cells, macrophages, as well as T cells and B cells involved in

adaptive immunity. They are also present in non-immune cells like epithelial and endothelial cells, as well as fibroblasts. The TLR family comprises TLR-1 to TLR-13, with TLR-2 and TLR-4 being recognized as the primary pattern recognition receptors (Kawai *et al.*, 2009) [20]. These TOLL and TLR family proteins share common features, such as an extracellular domain with leucine-rich repeats and an intracytoplasmic region containing a TOLL/interleukin-1 receptor (TIR) homology domain. TLRs play essential roles in initiating both adaptive and innate immune responses. When an infection occurs, antigen-presenting cells (APCs) like macrophages and dendritic cells express TLRs on their surface. These TLRs then bind to pathogen-associated molecular patterns (PAMPs) and initiate a signalling pathway that triggers the host's defence mechanisms by inducing reactive oxygen species (ROS) and reactive nitrogen species (RNS). TLR-2 and TLR-4 activate the production of pro-inflammatory cytokines mediated by extracellular heat shock proteins (HSPs) through the NF-kB pathway. (Zhang & Ghosh, 2001) [21]. Studies on immune profiles in peripheral blood mononuclear cells (PBMC) of local Bama miniature pigs exposed to 21 days of heat stress have shown an upregulation of TLR-2 and TLR-4. These receptors are involved in recognizing conserved microbial molecules such as lipoproteins and lipopolysaccharides. Heat stress has also been found to upregulate the genes for TLR-2 and TLR-4 in human monocytes (Zhou *et al.*, 2005) [22]. In Black Bengal goats, research on seasonal influences on TLR 1-10 mRNA expression revealed a significant increase in TLR gene expression during the summer season (Paul *et al.*, 2015) [23]. In Tharparkar cattle, TLR-4 and TLR-2 mRNA expressions were substantially higher during heat stress. Furthermore, heat stress has been shown to upregulate the expression of HSP70, TLR-2, and TLR-4 in monocytes (Bharti *et al.*, 2017) [24].

Effect of heat stress on acquired immunity

Th1 cells are primarily involved in the cell-mediated immune response, while Th2 cells are responsible for the humoral immune response. The modulation of cytokine gene expression can shift the immune function from Th1 to Th2 and vice versa. Th1 cells release cytokines like IFN-γ, IL-2, and TNF-β, contributing to cellular immunity. Th2 cells, on the other hand, produce cytokines such as IL-4, IL-10, and IL-13, which support humoral immunity. IL-12, in combination with IFN- γ, can convert uncommitted T helper (Th0) cells into Th1 cells, while cytokines IL-4 and IL-10 promote the production of Th2 cells. It's important to note that Th1 and Th2 cell-mediated responses can inhibit each other (Elenkov & Chrousos, 1999) [25]. Glucocorticoids inhibit the release of major Th1-related cytokines, IL-12 and IFN- γ, which are involved in cell-mediated immunity (Elenkov *et al.*, 1996) [26]. Additionally, glucocorticoids downregulate the expression of IL-12 receptors in Th1 cells, leading to a shift in immune function from Th1 to Th2 (Wu *et al.*, 1998) [27].

Dendritic cells are potent antigen-presenting cells that bridge the gap between innate and adaptive immune responses. They play a key role in phagocytosis and antigen presentation and express higher levels of MHC Class II and co-stimulatory molecules like CD80, CD83, and CD86 on their cell surface. Glucocorticoids inhibit the expression of these molecules on dendritic cells, thereby preventing their maturation (Girndt *et al.*, 1998) [28]. Additionally, catecholamines, including adrenaline and noradrenaline, are released during stress conditions and can inhibit the production of IL-12, the development of Th1 cells, and the differentiation of Th2 cells (Elenkov *et al.*, 1996) [26]. Treatment with adrenergic agonists has been found to inhibit the production of IFN- γ by Th1 cells (Sanders *et al.*, 1997) [29].

Immunological biomarkers for heat stress

1. Heat Shock Proteins (HSPs)

Heat shock proteins (HSPs) are a group of proteins produced by cells in response to stressful conditions, and their discovery is credited to the Italian geneticist Ferruccio Ritossa in 1962 while studying Drosophila at the Genetics Institute in Pavia. HSPs play a vital role when elevated temperatures or other stressors have adverse effects on cell structure and function. They are highly conserved proteins that act as molecular chaperones, aiding in thermotolerance and the cell's ability to withstand damage, such as oxidative stress (Archana *et al.*, 2017) [30]. The expression of HSPs is regulated by heat shock factors (HSF), which are endogenous. The HSP family includes various important proteins, with HSP70 being the most prominent, influencing diverse biological systems and holding therapeutic potential (Shrestha *et al.*, 2016) [31]. In a stressed environment, HSPs interact with misfolded proteins, preventing the formation of toxic protein aggregates and helping to maintain the cell's protein balance (Vabulas *et al.*, 2010) [32]. Upon exposure to heat, the heat shock transcription factor dissociates from HSPs in the cytoplasm and binds with other HSF monomers to form trimers before moving into the cell's nucleus. These trimeric HSFs bind to heat stress elements (HSE) in the nucleus, triggering gene transcription and leading to the hyperphosphorylation of target genes related to heat stress, thus increasing the production of HSP mRNA (Collier *et al.*, 2008) [33]. HSP70i, an inducible variant of HSP70 with a molecular weight of 70kDa, has been suggested as a predictor for cellular heat adaptability in cattle (Jose *et al.*, 2022) [34]. Yadav *et al.* 2015 [35] demonstrated an increase in HSP-70 and HSP-90 during stress in goats, while similar findings were reported by Bharati *et al*, 2017 [24] in Tharparkar cattle.

2. Acute Phase Proteins (APPs)

Heat stress can have a notable impact on the production and regulation of acute phase proteins (APPs) in the body. APPs are a group of proteins that the body synthesizes in response to various inflammatory stimuli, including infection, injury and tissue damage. They play a vital role in the innate immune response and help modulate the inflammatory process. Positive APPs, like C-reactive proteins (CRP), haptoglobin, and serum amyloid A (SAA), show a significant increase in their serum concentrations in response to infections and inflammations. Conversely, negative APPs, such as albumin and transferrin, exhibit decreased serum concentrations in reaction to infection, inflammation, and stress (Mittelman *et al.*, 2018) [36]. Cui Y *et al.* 2019 [37] found that haptoglobin (HP) concentrations increased during chronic stress in pigs. Similarly, Marco-Ramell *et al.*, 2012 [38] observed elevated levels of SAA, CRP and HP during periods of stress in cattle.

3. Nitric oxide (NO)

Nitric oxide (NO) is a crucial cellular signalling molecule with a wide range of functions. It plays a role in regulating vascular tone, insulin secretion, airway tone, and peristalsis, and is involved in processes like angiogenesis and neural development (Król *et al.*, 2020) [39]. Notably, NO is highly

diffusible and not limited to the site of its production. Both inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) have been identified in various immune cells, including macrophages, natural killer (NK) cells, and dendritic cells (Ghasemi *et al.*, 2022) [40]. Heat stress can trigger the expression and activity of inducible nitric oxide synthase (iNOS), leading to an increased production of nitric oxide (NO) in certain tissues (Förstermann and Sessa, 2011) [41].

Conclusion

In the context of global climate change, heat stress stands out as the primary stressor impacting livestock production. The interaction between stress hormones and cytokines plays a significant role in altering immune functions during heat stress. Heat stress has the effect of suppressing innate immune function by compromising the integrity of skin and mucosal barriers and reducing the proliferation of immune cells. Moreover, heat stress also affects the highly specific adaptive immune mechanisms. More specifically, heat stress deteriorates the cell-mediated immune responses. Overall, heat stress compromises the innate and acquired immunity of livestock, making them more susceptible to infections and diseases. This vulnerability can lead to reduced productivity and increased morbidity and mortality rates in affected animals. Mitigating the effects of heat stress through appropriate management practices, such as providing adequate shade, ventilation and access to clean water, is essential to maintaining the health and well-being of livestock in hot environments. Additionally, breeding for heat tolerance and genetic selection can help enhance the immune response of livestock in the face of heat stress.

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