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Review Article

The impact of heat stress on the gastrointestinal tract integrity of poultry

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ABSTRACT

Heat stress (HS) endangers the quality and yield of poultry products and compromises the sustainability of poultry production. Birds are particularly sensitive to HS due to the absence of sweat glands, limited respiratory and cardiovascular systems development, and increased metabolic rates. The gastrointestinal tract (GIT) is one of the main organs affected by HS via numerous pathways, including organ ischemia and hypoxia, resulting from superficial vasodilation and excessive panting. Additionally, HS damages epithelial cells, negatively affects the GIT function in nutrient resorption and digestion, causes immunosuppression, destroys microbial balance, and damages the intestinal barrier and microstructure. Thus, HS disrupts intestinal homeostasis and induces gut permeability (leaky gut), causing systemic inflammation and infection. Heat stress induces the disruption of tight junctions and oxidative stress by the overproduction of reactive oxygen species (ROS), damaging intestinal tissues. Heat stress decreases the creation of digestive enzymes owing to high levels of ROS that augment lipid peroxidation. Increasing the production of heat shock proteins can be considered a sign of intestinal tissue injury. This review aims to deliver a profound view of the effect of thermal stress on the integrity and function of the gastrointestinal tract.

1. Introduction

Over the latest decades, climate change has resulted in further hot days with more frequent and intense unexpected heat waves [1]. One area of human life that may be severely impacted by global warming is livestock production, particularly the production of poultry, a significant source of food for humans. Heat stress (HS) is a veritable challenge in poultry production and a growing problem for researchers on food safety and global warming. The poultry business suffers annual financial losses as a result of HS [2]. Birds that are exposed to high temperatures suffer from illness and mortality at a high rate, endangering human nutrition [3]. Therefore, HS becomes a significant barrier to the future development of the poultry business, particularly in the hot regions of the world [4].

Poultry has a substantial contribution to nutrition and food security. Birds are sensitive to heat stress owing to high metabolic activity and lack of sweat glands [5]. The adverse HS effects can damage some organs including the gut. The gut plays a main role in nutrient transport, digestion, and absorption, yet it is very susceptible and responsive to HS. Heat stress causes unfavorable influences on immunology, microbiology, and physiology, resulting in impaired and abnormal GI in birds [6]. Such influences can lead to a generalized exacerbation of digestive functions, leading to decreased productive performance and poor health conditions due to low nutrient intake and high mucosa permeability. High ambient temperatures can change physiological responses of birds that indirectly or directly adversely affect their production [4]. Some investigations point out that heat stress changes gut permeability via disrupting tight junction (TJ) proteins [7]. Some of these changes caused by HS are related to the secretion of proinflammatory cytokines and neurotransmitters in the gut and brain, with profound impacts on intestinal physiology [8]. Additionally, these changes further encourage the immune system through toll-like receptors (TLRs) signaling and heat shock proteins (HSPs), causing initiation of injury and inflammation and alterations in intestinal mucosal microstructure [9].

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Under heat stress, some physiologic and morphologic alterations are detected in the gastrointestinal tract (GIT), affecting the integrity and functionality of the intestinal epithelium, alteration in intestinal microflora, disruption in blood flow of GIT, and worsening in intestinal morphological indices [10,11]. Gut health should be treated holistically by observing the main elements, which synergistically affect it, including the GI microbiota, GI immune system, and GI epithelium [12,13]. Furthermore, Patra and Kar [14] stated that HS prompts various alterations in the GIT including augmented oxidative insults, microstructures injuries of the mucosal epithelia, immunity reduction, and high permeability of GIT to pathogens and toxins. Therefore, this review provides an objective overview of the available scientific evidence about the impacts of HS on the integrity and function of GIT and their effect on intestinal development, microbiota, oxidative stress, heat shock proteins, digestive enzymes, and immunity function in GIT of poultry.

2. An overview of heat stress

Heat stress is a significant concern in poultry production worldwide, the deleterious impacts of which are likely to be further aggravated by continued global warming. Identification of harmful influences is necessary to solve the problem during HS. Heat stress influences egg and meat production of poultry, as well as flock well-being and health, through the main alterations in the gut microbiota and intestinal physiology [2,15]. Heat stress can be defined as a condition where birds cannot maintain a balance between body heat dissipation and production. It can be classified into two classes [16]: (1) Acute HS means a rapid and short rise in temperature. (2) Chronic HS refers to extended exposure to high temperature (prolonged and continued period). Optimal environmental conditions for chicken performance range from 18 to 22°C, with an internal (body) temperature of 40.6-41.7°C [17]. However, under chronic or acute HS conditions, the body temperature of birds may reach up to the lethal limit (45-47.2°C) [18]. According to Goel [19], chronic heat stress leads to the excessive generation of reactive oxygen species (ROS), which further results in oxidative injury, but acute heat stress results in the production of ROS that was then neutralized by antioxidant enzymes (Figure 1). The harmful HS effects can range from discomfort to damage to multiple organs to death by spiralling hyperthermia [2]. Avian species possess some mechanisms including evaporative, convection, and radiant cooling through perspiration and vasodilation to maintain homeostasis and lower body temperature [20]. Changes in the intestine's structure and function as well as the composition of the gut bacteria are both intimately tied to heat stress [21]. Cell damage occurs in the gut as a result of the reduced oxygen and nutrient availability caused by prolonged exposure to high ambient temperatures. Ultimately, the gut barrier becomes deteriorates to the point where the constituent of bacteria and endotoxin in the intestine enters the body. The presence of endotoxin prompts an overstated inflammatory response from the immune system in the gut, including the production of high levels of interleukin-1 and tumor necrosis factor [22]. These cytokines have some negative influences, such as blood clotting, blood leakage from capillaries, and cell death, which lead to the failure of many organs and then death.

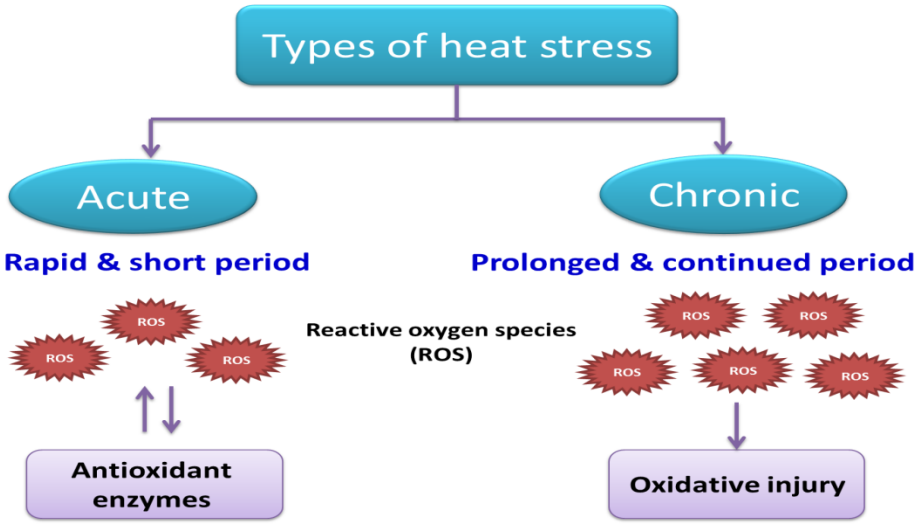

Fig. 1. Types of heat stress and their influences on production of reactive oxygen species in bird body.

3. Effect of HS on intestinal development

Coordination of functions, such as the regulation of mucus layer and metabolic regulation of epithelial cells, is necessary for the epithelial intestinal mucosa to maintain its functional integrity. Two related cytological processes contribute to the small intestinal mucosa development [23]: (1) cell renewal owing to differentiation and proliferation of columnar cells in crypts and along the villus and (2) the normal loss of cells through extrusion at villous apices after they have undergone apoptosis. The intestinal mucosa is a significant biological, chemical, and physical barrier that isolates the external environment [24]. It is generally recognized that intestinal damage particularly weakened intestinal integrity and barrier function, is the main reaction to heat stress [11]. Any intestinal barrier stress results in increased blood antigen permeability, triggering inflammation [25].

Uni et al. [26] clarified that heat stress causes alterations in intestinal development by decreasing the proliferation rate of enterocytes, the number of villi, and the small intestine weight. High temperatures have been demonstrated to have a deleterious impact on intestinal growth, leading to villous

atrophy, injury to the mucosal epithelial cells, reduced function of the mucosal barrier, and changed microbiota composition [27,28]. Heat stress can impair the barrier integrity and intestinal morphology of chickens [29], which reduces their ability to digest and absorb food and increases their permeability to luminal antigens and toxins. The exposure to heat stress significantly declined both the number of proliferating cell nuclear antigen-positive cells and the villus height/crypt depth ratio in the duodenum and augmented the endotoxin concentration in plasma [30]. Sandikci et al. [31] indicated that heat stress diminished the number of mucus-producing goblet cells placed in the ileum villi. Ashraf et al. [32] revealed that high environmental temperatures for 21 days (35 ◦C) induced severe injury in the gut, leading to significant alterations in the morphometric indices of jejunum and duodenum of broiler chicks. Santos et al. [28] illustrated that broilers exposed to HS had reduced epithelial cell area and augmented the width of villi base in the intestinal mucosa. Yamauchi et al. [33] pointed out that morphological alterations occur more rapidly in response to stress in the proximal two-thirds of the small intestine than in the ileum.

The intestinal mucosa is damaged by heat stress challenge, which may also be brought on by a decrease in the epidermal growth factors (EGF) in the intestine [34]. EGF, a mitogen, has been demonstrated to enhance intestinal morphology and epithelial recovery in the mucosa by promoting enterocyte proliferation and differentiation [35]. Numerous investigations have noted a decline in the mRNA and protein expression of EGF or EGF receptors in the gut as a result of HS, which may be the cause of the decline in enterocyte cell proliferation and, subsequently, the length and depth of the villi and crypts [34,36].

The mitotic divisions in the crypt contribute about 60% of epithelial cell proliferation, followed by the middle and apical regions of the villus (32% and 8%, respectively). It is expected that alterations in cell proliferation would first emerge in the stem cells of crypt rather than in the villus due to the high proliferative activity of the crypt. Broiler chicks devote about 12% of their synthesized protein to GIT tissue turnover [37]. As a result, the intestinal morphology restructuring owing to HS has noteworthy influences on the gut catabolic and absorptive roles. The alterations in intestinal morphology may be attributed to the direct HS influences on the intestinal epithelia, for instance, lowered antioxidant status and hypoxia or indirectly via alterations in gut microbs, which control mucosal cell differentiations. Damage to gut morphology is one of the first HS results and depends on the stressor duration and intensity. Marchini et al. [23] stated that acute heat stress reduced enterocyte proliferation and crypt depth, without affecting villus height, but chronic stress diminished jejunum weight and villus height. These alterations affect the ability of birds to absorb and digest the nutrients necessary for the production and maintenance of life.

4. Effect of HS on tight junctions of the gut

Gut epithelial cells adhere to each other through tight junctions (Figure 2). Tight junctions are paracellular and transcellular proteins that enable substances to move passively across the epithelium in response to a gradient in their concentration [38]. Paracellular junctions are strictly controlled in thermal neutral conditions [39]. Under heat stress, the TJ barrier becomes compromised and luminal constituents leak into the blood stream, leading to a "leaky gut" that refers to a condition that causes chronic systemic inflammation and needs high energy resources that influence adversely the birds [40]. Ilan et al. [41] indicated that changes in gut permeability are linked to bacterial translocation in the systemic and/or portal circulation in some types of leaky gut syndromes that result in systemic bacterial infections. This signifies that heat stress leads to dysregulation of intestinal barrier function and encourages leaky gut by the change of TJ proteins that deserves further in-depth investigations. Elevated temperature reduces the integrity of the tight joint and boosts the pathogen's permeability, the levels of hormones answerable for reducing appetite in birds [29,42,43].

Patra and Kar [14] indicated that TJ proteins are considered border protectors and gate guards made by claudins (CLDN), zonula occludens (ZO), junctional adhesion molecule (JAM), and occludin (OCLN) proteins that control the passage of molecules through selective paracellular pores, in particular avoiding the entry of endotoxins compounds and pathogenic bacteria. The role of TJ alters owing to HS as demonstrated from decreased mRNA expressions of TJ genes, and their proteins along with alterations in regulatory proteins in some investigations, however, the alterations depend on the heat exposure period and intensity. The expressions of JAM-A, ZO1, and OCLN in the ceca and ileum were decreased in heat-stressed hens (33℃ for 20 days) compared to control hens (26℃) [44]. In broiler chickens, HS (30-33℃/8 h/day vs. 20℃) declined mRNA CLDN3 abundance, but not mucin 2 (MUC2), OCLN, CLDN2, and ZO1 in the jejunum [45]. The expressions of CLDN-1, ZO-1, and OCLN genes were diminished in heat-stressed chickens [42]. The increase of pathogenic bacteria due to HS in the intestine leads to leaky gut syndrome [46]. Finally, it can be said that HS negatively affects intestinal integrity and permeability by changing the intestinal morphology and epithelium junctions' integrity (Figure 2).

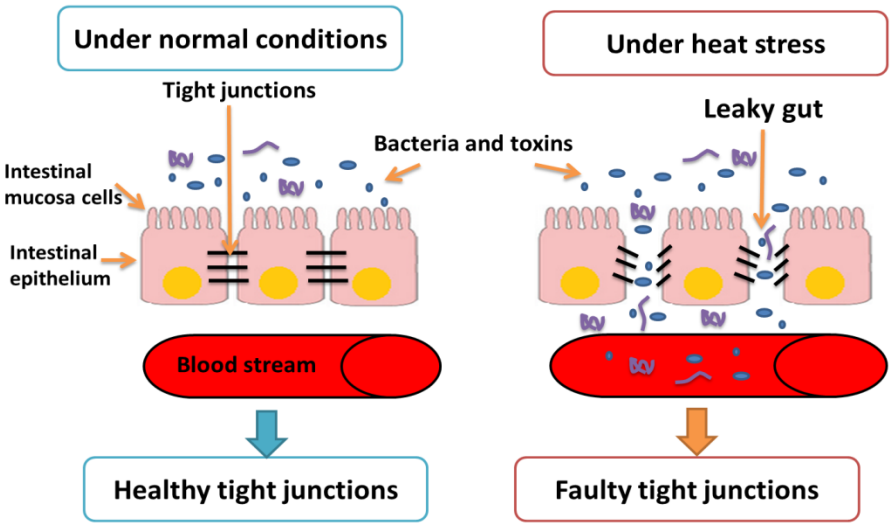

Fig. *2*. Impact of heat stress on tight junctions and intestinal integrity in poultry.

5. The suggested mechanisms for the effects of HS on the intestinal epithelium

There are two mechanisms suggested forth as to how heat stress affects the intestinal epithelium. The first is that types of reactive nitrogen and/or oxygen species are created in response to heat stress and augmented oxidative activity, overwhelming the ability of endogenous antioxidant systems [47]. The creation of these free radical molecules causes damage to the epithelial cell membranes when chicks are exposed to heat, which reduces the number of tight junctions (TJ) and the expression of TJ genes. As a result, the intestinal barrier is permeable to bacterial endotoxins entering through paracellular pathways. The second mechanism is that heat stress encourages the proinflammatory cytokines generation (e.g., tumor necrosis factor-α (TNF-α) and interleukin-2 (IL-2)), which likewise injure TJ [48]. Hoyer et al. [49] clarified that IL-2 is created via T cells, and once released; it stimulates other types of cells such as macrophages that then secrete proinflammatory cytokines, like TNF-α, to start inflammation. Additionally, Costalonga and Zell [50] elucidated that the IL-2 secretion could be promoted via endotoxins; therefore, this mechanism might be an indirect or secondary influence. To maximize the dissipation of sensible heat under HS, a significant amount of blood is diverted from the splanchnic tissues to the periphery of the body [51,52]. This is another evolutionary-preserved adaptation of the cardiovascular system. Due to a sympathetically induced vasoconstriction of the viscera, the increased blood pressure is largely compensated for, which harms the GIT [15].

6. Effect of HS on gut microbiota

The poultry gut harbors a variety of microorganisms that support the breakdown of complicated nutrients into simple forms that can be readily absorbed and digested [53,54]. Heat stress has a noteworthy influence on the intestinal microbial community of poultry. The heat stress impact on the gut microbiota composition can directly result from changing body temperature or indirectly owing to a gradual or acute alteration in the birds' intestinal integrity, physiological status, behavior, and immune system activity [55]. The gut provides places for bacteria to colonize and flourish, and as a result, commensal microbes compete with pathogenic microbes for nutrients and space to live and create metabolites that enhance host intestinal immunity and slow the growth of pathogens, which together safeguard the gut epithelium. Brugaletta et al. [56] stated that high temperatures can be a "dysbiogenic stressor" that disrupts the hostmicrobiota interrelationship and weakens gut functionality. However, stressful stimuli can change the microbiome and damage intestinal barrier integrity at the same time [57]. Intestinal pathogens get access to the host circulation once the mucosal layer has been breached, which allows them to cause illnesses and reduce the efficiency of nutrient digestion and assimilation [58]. Heat stress declined populations of valuable bacteria (*Bifidobacterium* and *Lactobacillus*) in the intestine that was substituted by detrimental bacteria (*Escherichia coli*, *Salmonella sp.*, *Clostridium sp.*, and *Coliforms*). This unbalanced gut microbiota may distort the regulation of intestinal epithelial restitution, epithelial cell turnover, and tight junctions' reorganization [59] (Yu et al., 2012). Burkholder et al. [10] detected that HS significantly diminished the gut bacterial populations of birds. Neurohormones linked to stress can induce the growth and expression of virulence factors in pathogenic bacteria within the lumen [60].

Enhanced intestinal permeability resulting from HS allows pathogens penetration through GIT. The increased proportion of enteric pathogenic bacteria leads to reduce the immunity in heat-stressed birds. Moreover, the detrimental bacteria colonization begins in the crop and intestine leading to changes in lymphoid organs [61]. The exposure to heat (30°C for 24 h) changed the microbial community composition in the cecum and ileum of chickens [10]. Broiler chickens exposed to HS (33°C/10 h vs. 22°C) had lower numbers of *Bifidobacterium* and *Lactobacillus*, and higher numbers of *Clostridium* and *Coliforms* in the small intestine [21]. *Lactobacillus* counts were reduced owing to HS (26°C vs. 33°C/20 days) in the cecum and ileum of laying hens but the number of *E. coli* was diminished in the ceca and ileum of laying hens [44]. Additionally, Tsiouris et al. [62] revealed that HS can encourage the growth of *Clostridium perfringens* in the intestine of chicken, acting as a risk factor for outbreaks of necrotic enteritis in flocks raised in

hot environments. Along with other hazardous bacterial effectors, *C. perfringens* can release enterotoxins that may impair gut barrier functions and TJs [63]. Indeed, intestinal inflammation gives the HPA axis feedback, which in turn controls the immune system's response against pathogens [64]. Heat stress can damage mechanisms of homeostasis and subsequently impact the composition of gut microbiota through inducing stress hormones and neurotransmitters that modify gut physiology [14,65]. This signifies that HS stimulates HPA axis and raises corticosterone concentrations that may reduce the activity of the intestine's immune system, and alter the composition of the microbiota. Finally, HS lessened beneficial microbiota and augmented pathogenic bacterial populations in the gut.

7. Effect of HS on oxidative stress in the gut

Physiologically, reactive nitrogen species (RNS) and ROS are created by epithelial cells of GIT either by enteric commensal bacteria or from oxygen metabolism, affecting the regulation of gut health [66]. With exposing birds to HS, oxidative stress relates to the generation of ROS causing cell disruption [67]. The deprivation of energy and oxygen during HS creates ROS within gut cells [68]. These damaging molecules harm the ability of ion pumps to maintain cellular ion homeostasis, and attack cell membranes, starting chain reactions that rapidly damage membrane integrity and cell structure [22]. Heat stress can cause oxidative stress and impaired gut flow, leading to the intestinal epithelium injury and microflora variations, as a result of affecting related disturbances in the antioxidant system [23,69]. As the first route of protection against oxidative stress, the gut mucosa contains an extensive antioxidant defense system such as glutathione peroxidase (GSH-PX), SOD, glutathione (GSH), and CAT [70]. Both SOD and GSH are intracellular antioxidants, broadly spread in the small intestine, and their abundances are at a greater level during intestinal development [71]. The cell has two key defense mechanisms against ROS: GSH, which destroy ROS, and heat shock proteins (HSPs) that repair proteins that have been injured by ROS. GSH is the most main antioxidant in the body and is necessary for normal intestinal functions. During heat stress, GSH not only protects gut cells against ROS, but is necessary for HSPs activation [72]. In order to deliver adequate protection, the GSH cycle needs a sufficient supply of sulfur and selenium. The reduced level of antioxidant enzymes may be associated with the insufficient defense of immune cells from the oxidative stress that increases during HS [73]. Marchini et al. [23] indicated that oxygen free radicals, including hydroxyl radicals and superoxide anions, are participated in the pathogenesis of chronic and acute stress-prompted GIT damage, and can lead to lipid peroxidation. Heat challenge usually augmented malondialdehyde (MDA) and diminished antioxidant enzyme activities, e.g., SOD, GSH-PX, and CAT in the intestine, leading to structural changes and damages in the mucosa, and impaired barrier integrity. Chronic cyclic HS (32-33ºC for 8 h/day vs. 20ºC) for 6 weeks augmented jejunal mucosal MDA, and depressed SOD activity in ileal mucosa in chickens [45]. Cyclic HS (32ºC, 10 h/day vs. 22ºC, 24 h/day) in chickens for two weeks augmented MDA content in the small intestine [74]. According to studies that concentrated on the GIT, oxidative stress weakens the TJ-regulated paracellular barrier and raises intestinal permeability [75]. Free radicals and oxidative stress induce disruption of the tight junctions in the GIT, resulting in alterations in protein tyrosine-phosphatase and tyrosine kinase activities, and adjusting the phosphorylated state of TJ proteins [76]. Tan et al. [77] stated that HS can reduce the mitochondrial respiratory chain activity following ROS overproduction and oxidative damage.

8. Effect of HS on gut hormones

Some investigations have stated that several GI hormones, such as gastrin (GAS), cholecystokinin (CCK), ghrelin (GHR), glucagon-like peptide1 (GLP-1), neuropeptide Y (NPY), peptide YY, and biogenic amines (e.g. serotonin), participate in the feed intake modulation in both mammals and birds [78,79]. Prolonged heat exposure changes the brain–gut neuropeptide expression in birds [80,81]. Therefore, understanding the differences in the number of enteroendocrine cells (EECs) expressing some biogenic amines and hormones participating in the regulation of feed intake can help identify key physiological mechanisms by which high environmental temperatures adversely affect feed intake and the productive performance of broiler chicks. Mazzoni et al. [82] stated that HS affects the distribution and presence of EECs, signifying that some GI biogenic amines and peptides may be implicated in the regulation of voluntary feed intake and appetite in heat-stressed broiler chicks. Also, HS significantly boosted the number of EECs expressing NPY and GHR in the proventriculus, and CCK and GLP-1 in the small intestine (jejunum and duodenum) [82]. Chowdhury [81] demonstrated that the reduced feed intake related to HS was reflected by the upregulation of a hypothalamic NPY precursor at the transcriptional level. In comparison to thermoneutral conditions, HS induced a slightly increased hypothalamic NPY gene expression in laying hens [80].

9. Effect of HS on digestive enzymes

Production of digestive enzymes in the gut lumen is declined due to HS that negatively impacts the intestinal mucosa and causes inflammation and oxidative stress [83]. Patra and Kar [14] revealed that nutrient digestion in the gut may be impaired owing to lowered digestive enzymatic activity, changed expressions of the nutrient transport genes and proteins, damage to the mucosal structure, and lowered surface area for absorption. Heat stress decreases the creation of digestive enzymes, i.e., amylase, chemotrypsin, trypsin, maltase, and sucrose owing to the high levels of ROS that augment lipid peroxidation of cell walls of the pancreas and intestine. Hence, it harmfully affects nutrient digestion and absorption while affirmatively affecting the gut sensitivity to pathogens [28,45]. Thermal stress may decline the secretion of digestive enzymes motility of the digestive system, and blood flow to the intestine, affecting nutrients digestion, absorption, and metabolism [10]. The activities of chymotrypsin, trypsin, and amylase in the intestinal juice and digesta passage were reduced in broiler chickens exposed to high temperature (32ºC vs. 20ºC) [28]. Furthermore, HS raised Na+/K+-ATPase activity in the gut that was probably owing to maintaining the osmotic homeostasis in the intestine [84].

10. Effect of HS on immunity function of gut

Around the body, the immune system has many lymphoid organs. There are numerous related to the intestinal lumen, including various lymphoid cells found in the lamina propria and the epithelial mucosa (intraepithelial lymphocytes) besides specialized lymphoid structures, for instance cecal tonsils, bursa of Fabricius, Meckel's diverticulum, and Peyer's patches [15,85]. The gut neurons and intestinal immune cells share information to address any stressor through combined actions [86]. As the immune system suffers due to HS, the dangerous microbes in the intestine grow and colonize causing morphological alterations in lymphoid cells of the gut. Heat stress modifies the immune responses of poultry to invading pathogens via altering the pro-inflammatory cytokines and Toll-like receptors. In avian, HS from 35 to 41 days of age (31ºC) augmented Salmonella invasion and colonization to the cecum, and depressed avian beta defensin (AvBD4), TLR2, IL10, IL1B, and transforming growth factor β-1 in cecal tonsils of chicks challenged with Salmonella Enteritidis [61].

11. Effect of HS on heat shock proteins (HSPs) of gut

HSPs are intracellularly combined, excessively pervasive, and conserved proteins that are activated via some stress elements. In other words, HSPs are well-recognized as molecular chaperones and stress proteins that safeguard the internal cell environment through contributing to protein repair, folding, degradation, and localization influencing necessary processes for instance regulation of cellular redox conditions, transcription, cell signaling, metabolism, and protein synthesis, and therefore regulating cell survival and growth [87,88]. HSPs have a vital function in protein homeostasis regulation and are considered general signs of tissue damage [89]. Heat stress harmfully affects the immune system through provoking the stimulation of HSPs that leads to poor energy and cellular respiration [90], reducing the productive performance of chicks. The upregulation of HSPs, mainly HSP70, gives a preventive mechanism via inhibiting pro-inflammatory cytokines expression [9]. Ahmad et al. [83] illustrated that HSP70 has a significant cytoprotective function in the intestinal epithelium, as well as a function in intestinal barrier formation. Furthermore, under a thermal ambient environment, it regulates and strengthens normal intestinal TJ and forms an effective intestinal barrier in the bird ileum. Besides, the fundamental and prime function of HSP60 under various stress factors is cell protection through the regulation of the mitochondrial protein collecting process [91]. Also, HSP60 is a well-known helper in cell mitochondria and normalizes the mitochondrial bilayer membrane to counteract cellular injury [92]. HS (38-39ºC, 8 h/day for 5 days vs. 22-23ºC) upregulated HSP90, and HSP70 mRNA expressions in the jejunum of chicks [88]. Finally, HSPs play a key function in the safeguard of intestinal mucosal integrity from HS harm by protein repair and keeping them functional, boosting the antioxidant capacity, and preventing lipid peroxidation, thereby contributing to cellular functions under stressful environments.

12. Conclusion

Heat stress causes harmful effects on birds, the most important of which is damage to the cells of the alimentary canal and a decrease in the length and depth of the villi and crypts - as well as a defect in the intestinal barrier function and stimulates intestinal leakage - it also affects the intestinal epithelium. On the other hand, increased hypothalamic NPY gene expression in laying hens negatively affects the intestinal mucosa, causes inflammation and oxidative stress, and modulates the immune response to invading pathogens by altering pro-inflammatory cytokines and spotter-like receptors. HSPs are well-recognized as molecular chaperones and stress proteins.

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Author Contributions

All authors contributed to this work.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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