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The role of gut microbiome agility on chicken viral immunity, gut-brain axis during heat stress: a comprehensive review

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Abstract: Background: The poultry industry faces significant annual financial losses due to heat stress, which also poses risks to the health and wellbeing of the birds. including other animals, chickens that are exposed to high ambient temperatures have a variety of physiological changes. These include behavioral changes including stopping to eat, the start of a stress signaling cascade, and immunological and inflammatory reactions in the intestines. The neurological and humoral systems connect the brain and gut, facilitating two-way communication. This network is referred to as the gut-brain axis. Furthermore, heat stress modifies the makeup and abundance of the microbiome in addition to causing hyperthermia and oxidative stress at the gut epithelium, which reduce permeability and increase susceptibility to infection and inflammation. Similar routes are used by the gut microbiota to communicate and control host metabolic balance, health, and behavior. These pathways are mostly mediated by metabolites generated by bacteria as well as hormones and neurotransmitters. It follows that altering the gut microbiota's makeup will influence intestinal health and alter host brain circuits through a variety of complimentary and reinforcing ways. We outline the composition and operation of the microbiota-gut-brain axis in this review, focusing on the physiological alterations that transpire in chickens during heat stress.

Keywords: gut microbiome agility, chicken viral immunity, gut-brain axis, heat stress

Introduction: The microbiota-gut-brain axis (MGBA) has been extensively studied for decades in both human and animal species because of its critical involvement in the pathophysiology of many neurodevelopmental and neurodegenerative illnesses as well as in maintaining homeostasis (Cryan et al., 2019). Furthermore, the significance of this axis in non-mammalian species—like chickens—has been recognized, and possible mechanisms are being looked at. It is believed that rather than being commensal, the relationship between the gut microbiota and host is mutualistic (De Palma et al., 2014). The microbiome gets friendly habitats and undigested food from the host, and these microbes metabolize and produce neuroactive substances. Certain neuroactive chemicals, like 5-HT, enter the blood or interact with the immunological and enteric nervous systems, respectively, to regulate

host physiological processes either locally or systematically. Certain factors affect host behaviors by acting on the central nervous system (CNS), such as through vagal afferents, while other factors cause structural and functional alterations in the intestine (Villageliũ and Lyte, 2017). Depending on the kind and degree of variables, such as food composition, environmental cues, host genetics and phenotypes, and environmental stressors, the gut microbiota's interaction with the host may be advantageous or harmful (Kers et al., 2018).
Simply put, stress is an organism's adaptive physiological and psychological reaction to reestablish homeostasis (Glaser and Kiecolt-Glaser, 2005). According to reports, the digestive tract is implicated in how the body reacts to a variety of stimuli, including heat stress (Rostagno, 2020). When there is an imbalance in the net amount of heat energy produced by and released by an organism, heat stress—a serious environmental concern—occurs (Renaudeau et al., 2012), wherein the organism retains more heat than it can expend or use. Heat stress is intimately linked to modifications in the gut's structure and function as well as the makeup of the gut bacteria (Song et al., 2014; Sohail et al., 2015). There are few studies on how heat stress affects human gut microbiome (Karl et al., 2018), and a range of animal models are used to fully explore these impacts in order to offer therapeutic insights. We have focused on avian models in this review because it has been well documented that heat stress affects the gut microbiota and intestinal physiology of poultry, which in turn affects the production of meat and eggs as well as the health and welfare of the flock (Lara and Rostagno, 2013; Rostagno, 2020). However, more research is needed to completely understand how heat stress interacts with the gut microbiota of chickens and influences MGBA.
Here we review the literature on how heat stress affects the immune system, intestinal integrity, and microbiota, feeding and social behaviors in chickens, and physiological processes. We also focus on the connections between these changes and the composition of the gut microbiota. We also go over methods to lessen the negative impacts of high temperatures on avian behavior and health, as well as what is known about the use of probiotics and prebiotics as therapeutic and preventive interventions in animals under heat stress.

Microbiota-Gut-Brain Axis

Microbiome Composition

The various microorganisms that make up gut microbes include yeast, bacteria, viruses, other fungi, and protozoa. Most studies on gut microbiota have examined the makeup and roles of bacteria (Karl et al., 2018); Therefore, the focus of this review is bacteria. The microbiota content varies significantly throughout intestinal sites; in the small intestine, it is approximately 105 colony-forming units (CFU) per gram of digesta, whereas in the cecum, it is approximately 1011 CFU per gram of digesta (Xing et al., 2019; Rychlik, 2020). The last ten years have seen a surge in technology that has made it possible to profile microbiomes inside hosts. From enhanced laboratory culture methods to metagenomics and 16S rRNA gene sequencing, these advancements have allowed for a more in-depth and precise examination

of the microbiome's makeup. It is crucial to remember that comprehending the makeup of the microbiome does not always make it easier to comprehend its role and physiological effects. While Lactobacillus, Enterococcus, and Clostridiaceae predominate in the small intestine of chickens, Lactobacilli dominate numerous areas of the upper digestive tract, including the crop, proventriculus, and ventriculus (gizzard). Because gastric juices have a low pH, which supports Lactobacilli's dominance, the predominance of species is somewhat correlated with how the digestive organs work. The most prevalent phyla are Firmicutes, Bacteroides, and Proteobacteria in the cecal tonsils, which house digesta for the longest period during digestion and have a higher concentration of short-chain fatty acids (SCFAs) produced by bacteria than in other parts of the gastrointestinal tract (GIT) (Oakley et al., 2014; Villageliũ and Lyte, 2017; Karl et al., 2018; Rychlik, 2020).

Functions of Microbial Products

Microbial products can interact with immunological or neuroendocrine systems to affect host health and behavior, as well as act as an energy source for the host (Shenderov, 2016). After being absorbed, SCFAs can be utilized by intestinal cells, especially intestinal epithelial cells (enterocytes), as a metabolic substrate (ATP generation) (Bergman, 1990). Two important SCFAs, butyrate and propionate, work with G-protein-coupled receptors to control and preserve immune and energy homeostasis in cells, which in turn affects how active the cells are. They do this by triggering gene expression programming pathways that lead to apoptosis, chemotaxis, proliferation, and differentiation (Clarke et al., 2014; El Aidy et al., 2016). It has been shown that butyrate and acetate help to keep the GIT barrier intact, which inhibits bacterial colonization and translocation (Fukuda et al., 2011; Fachi et al., 2019). Furthermore, SCFAs function as signaling molecules and are directly linked to the manufacture of several neuroactive chemicals, including hormones, glucagon-like peptide 1, and leptin, which can be circulated to various parts of the brain. For example, these neuropeptide and neurotransmitter receptors allow neurons in the arcuate nucleus of the hypothalamus to receive signals, which are subsequently integrated to control the host's hunger (Tolhurst et al., 2012; Clarke et al., 2014; El Aidy et al., 2016).

Because they produce well-known neurotransmitters like 5-HT, which can operate locally or remotely via the nervous system or circulation, bacteria are sometimes referred to in the literature as "mind-altering" agents (Cryan and Dinan, 2012). 5-HT is produced in the intestine by host enterochromaffin cells, a subtype of entero-endocrine cells. Some tryptophan obtained from diets is turned into 5-HT, while the majority is processed in the liver via the kynurenine shunt. The stomach produces most of the body's 5-HT (>95%), which is produced by sequentially converting tryptophan through two enzyme processes. Then, intestinally generated 5-HT, whether bacterial or host-derived, can function through the vagus nerve or the endocrine system. The majority of 5-HT is released into the mucosa in the small intestine, and 2% of all enteric neurons are thought to be serotonergic (Mawe and Hoffman, 2013). Through several receptors, such as the metabotropic 5-HT1, 2, 4, and 7 and the ionotropic 5-HT3, 5-HT impacts vasodilation, inflammation, and the production of

chemicals during digestion, including bicarbonate, as well as gut movement (peristalsis) (Mawe and Hoffman, 2013).

Relationship Between Microbiota and the Host Gut

Microbial communities in the host GIT function well overall when things are normal and healthy. They produce extra vitamins, ferment undigested polysaccharides into SCFAs, and help preserve intact intestinal lumen surface structures in the face of pathogenic microbial species (Oakley et al., 2014). In fact, coprophagic animals—like rats and rabbits—recover these vitamins through eating feces. The host can develop a number of acute or chronic diseases as a result of the harmful effects of the gut microbiota going through dysbiosis, which can be brought on by or made worse by disturbances in the gastrointestinal environment (temperature, pH, nutrient composition, toxins, introduction of microflora, etc.) (Karl et al., 2018). For instance, there is evidence linking intestinal disorders like Crohn's disease and inflammatory bowel syndrome to dysregulated gut 5-HT availability and SCFA production (Oligschlaeger et al., 2019). Therefore, it is critical to the health and welfare of the host to maintain a hospitable mucosal environment and a healthy gut microbial community. A healthy community is typically defined as one that has a diversified microbiota in terms of both composition and genetic content, or one that is dominated by beneficial taxa (Karl et al., 2018).

Physiological Connections Between Gut Microbiota and the Host Brain

There are reciprocal relationships between the brain and gut microbiome. On the one hand, peripheral neurotransmitters and hormones can be obtained in significant amounts from the gut microbiome itself. In addition to the above-described modulation of gut activities like peristalsis, these chemicals also directly transmit the intestinal state to the brainstem and higher brain areas via vagal afferents. The hypothalamic-pituitary-adrenal (HPA) axis is activated by a variety of stressors via both peripheral and central routes. This may modify the makeup and activity of the gut microbiota in addition to the function of intestinal epithelial cells. Adrenocorticotropic hormone (ACTH) is released into the bloodstream by the anterior pituitary in response to the release of corticotropin-releasing factor (CRF) from the hypothalamus. This in turn causes the adrenal glands to release corticosteroids into the bloodstream, such as cortisol in humans and corticosterone in birds from the adrenal cortex. Through their direct interactions with intestinal immune cells, bacteria, and enteric muscle cells, corticosteroids have a wide range of effects on the gastrointestinal tract. These interactions result in the release of cytokines, which then operate on the brain to influence mood, hunger, cognition, and emotion through the bloodstream (Cryan and Dinan, 2012). Numerous external stimuli, including medications and food composition, can affect MGBA activity by feeding into these mutually reinforcing linkages through one or more pathways. For example, the brainstem and hypothalamus are two major brain areas that control hunger regulation. Gut-derived nutrients not only directly influence the microbiota, which controls the concentration of cytokines and neuroactive chemicals that impact brain activity, but they also trigger the release of satiety hormones like cholecystokinin (Petra et al., 2015).

Heat Stress

Stress responses are an organism's adaptive physiological and behavioral reactions to external demands or pressures. These reactions are the organism's means of attempting to maintain or restore equilibrium (De Palma et al., 2014; Karl et al., 2018). Stressors, also known as stressful stimuli, can range in intensity from mild to severe, and they can occur once or repeatedly. They can also be acute to chronic. Furthermore, different people's capacities for perceiving stress led to diverse consequences (Lucassen et al., 2014). People who are frequently in stressful situations seem to be at higher risk of developing gastrointestinal disorders.

Changes in the intestinal microbiota of chickens can be attributed to a variety of reasons. Features of the host, including age, breed, sex, and the GIT sampling site, are a significant source of these variables. The makeup of the microbiota is also influenced by environmental factors, such as temperature, location, feed, litter, housing quality, and biosecurity level (Kers et al., 2018). An increasing body of research suggests that heat stress is one of those environmental factors that significantly affects the composition of the intestinal microbiota and tissue structure.

Stressful environments include prolonged sun exposure, high relative humidity and temperature, and inadequate ventilation. These conditions cause disturbances to the internal energy homeostasis of birds, leading to physiological changes. Heat stress can arise from a temporary or persistent imbalance between the amount of heat released into the environment and the amount of heat produced internally by the animal. The range of ambient temperatures in which an animal effectively controls and maintains a consistent body temperature is known as the thermoneutral zone (Pollock et al., 2021). Animals are deemed to be exposed to heat stress when the ambient temperature rises over the upper critical temperature, which is the upper limit of the thermoneutral zone (McNab, 2002). For each of the first six weeks of life, the thermoneutral zones for broiler chickens are, in general, 28–34, 25–31, 22–28, 20–25, 18–24, and 18–24°C (Cassuce et al., 2013).

Surprisingly, exposure to high ambient temperatures raised core body temperature without significantly changing the bacteria in the cecal tonsils (Xing et al., 2019). But according to another study (Alhenaky et al., 2017) discovered that both acute and chronic heat stress increased rectal temperature in comparison to the thermoneutral condition, with the increase being even greater in the former case. During the first two days of heat exposure, the rectal temperature rose and then varied until it plateaued. Those who were experiencing heat stress thereafter displayed thermal homeostasis throughout the remainder of the observation period. When compared to the control birds, the prevalence of intestinal pathogens (Salmonella spp.) was higher in chicks exposed to heat (Alhenaky et al., 2017). These findings imply that although heat exposure can briefly alter core body temperature, it can be quickly changed and has little direct impact on the gut flora. But beyond the first few days, if the hens are subjected to consistently high ambient temperatures, their ability to adjust may be jeopardized, making them extremely vulnerable to heat stress.

As a result, heat stress can directly affect the composition of the gut microbiota through temperature changes, or it can indirectly affect it through abrupt or gradual changes in the behavior, physiological state, intestinal integrity, and immune system activity of the birds (See Figure 1), all of which will be covered in more detail in the sections that follow.

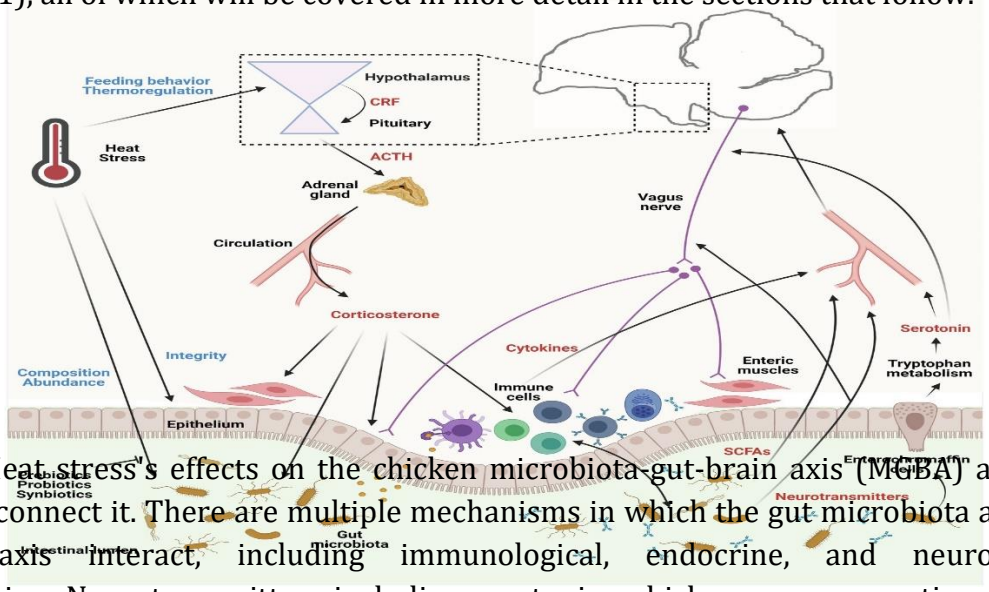

Figure 1: Heat stress's effects on the chicken microbiota-gut-brain axis (MGBA) and the routes that connect it. There are multiple mechanisms in which the gut microbiota and the gut-brain axis interact, including immunological, endocrine, and neurological communication. Neurotransmitters including serotonin, which can cause reactions in the vagus and enteric nervous systems, and short-chain fatty acids (SCFAs), which can nourish the host and control brain activity and behavior, are produced by the gut bacteria. Additionally, the gut microbiota encourages intestinal immune cells to produce and secrete cytokines that influence the brain and provoke both local and systemic immunological responses. Under certain conditions, such heat stress, the brain uses the same pathways to modify the composition and abundance of the gut microbiota. Both directly and indirectly, heat stress can have an impact on the MGBA. Heat stress activates the hypothalamic-pituitary-adrenal axis, which in turn helps birds produce corticosterone, which has additional effects on enteric cells and the gut flora. Prebiotics, probiotics, and symbiotics are viable strategies to mitigate the negative consequences of heat stress. CRF is corticotropin-releasing factor; ACTH is adrenocorticotropic hormone. This figure has been modified from earlier releases (Cryan and Dinan, 2012; Aoki et al., 2017) and created with BioRender.com.

Heat Stress Induces Appetite Suppression

Our team showed that young broiler chickens exposed to high ambient temperatures consumed less food. This was linked to changes in the activity of several peptides that regulate appetite, including anorexigenic CRF and orexigenic neuropeptide Y, both of which have peripheral effects on the HPA axis and enteric system (Bohler et al., 2020). Heat-exposed birds in another study on heat stress consumed more water, panted more frequently, and raised their wings for a significantly longer period (Mack et al., 2013). Although heat stress is linked to changes in nutritional absorption, notably in the case of amino acids and glucose, the drop in food intake that is often sustained during heat stress is believed to be a compensatory strategy to minimize heat production related with nutrient

metabolism. Because of this, dietary techniques to reduce nutrient-induced heat production have been used in several heat stress experiments involving chickens and other species. These techniques include creating meals with different macronutrient compositions (Chowdhury et al., 2021). Since the chicken's GIT uses up 7% of the energy from the diet, cutting back on feeding could have the unintended effect of offsetting some of the animal's heat production while also putting the animal's gut integrity and mucosal immunity in jeopardy. This would compromise nutrient assimilation, cause systemic inflammation, and hinder production (Thompson and Applegate, 2006; Deng et al., 2012).

In certain commercial operations, following hatching and processing, chicks must be transported over vast distances due to the distance between the grow-out facility and the brooder house. Delays in food intake after hatching can hinder the growth of the intestines, even if the leftover yolk sac serves as a storehouse of nutrients that the chick uses after it has hatched (Lamot et al., 2014; Proszkowiec-Weglarz et al., 2019, 2020; Qu et al., 2021), as well as the development of the microbiota (Flint et al., 2012). At a later age, similar effects were noted in response to food abstinence (Burkholder et al., 2008). Even for six hours, not having access to food makes viruses like Salmonella possible (Burkholder et al., 2008), to settle in the stomach and alter the microbial ecology (Thompson et al., 2008). Using sequencing techniques, the taxonomy of the gut microbiota was assessed. The results showed that the ileum and cecum of the hens that were denied food had different populations of Firmicutes and fewer Proteobacteria. Generally, the dominating families, including Turicibacteraceae, Ruminococcaceae, and Enterobacteriaceae, are the ones that are most affected by food deficiency on the intestinal microbiome (Metzler-Zebeli et al., 2019). Restricting food intake throughout life is a typical strategy among broiler breeders to meet goal body weights, which helps to prevent metabolic problems and enable optimal reproduction. But as previously said, these actions may have a detrimental effect on the chicken's gut microbiota, which may affect its overall health. Restricted access to nutrition, when coupled with exposure to high temperatures, may have significant effects on the bacterial makeup of the gastrointestinal tract and consequently alter the physiology of the bird.

Additionally, heat stress lowers the amount of food that layer-type chicks consume, produces fewer and lower-quality eggs, and increases the number of chick deaths (Mack et al., 2013; Mignon-Grasteau et al., 2015; Sahin et al., 2018). Heat exposure compromised the integrity of the gut mucosa in laying hens, which restricted the amount of nutrients that could pass through the intestinal mucosal layer (Zhang et al., 2017). Moreover, heat-stressed pullets and chickens have altered gut microbiome communities (Burkholder et al., 2008; Song et al., 2014; Zhu et al., 2019). Xing et al. (2019) discovered that layer chicks exposed to high ambient temperatures (29–35°C) showed changes in the composition of their microbiomes rather than species abundance, and that these changes were directly linked to reduced food consumption. In a further investigation, the layers were subjected to a 35°C cyclic temperature for seven hours each day. The results showed enhanced alpha diversity, meaning that after two weeks of exposure, the current species of the microbiome were

elevated in the cecum, albeit they eventually reverted to normal levels after four weeks (Hsieh et al., 2017). Furthermore, at the conclusion of the trial, the two most prevalent cecal phyla, Firmicutes and Bacteroidetes, had varying levels of richness. According to this study, heat stress began to alter the microbiota in layers at two weeks, but the bacteria didn't fully adjust to the temperature shift until four weeks later (Hsieh et al., 2017). Shi et al. (2019) discovered somewhat different outcomes and noted notable shifts in those two phyla's abundance beginning at one week, though there was also a decline in significance by four weeks. According to all these data, the amount and duration of heat exposure determine how heat stress affects the gut microbiota.

Elevated concentrations of numerous harmful taxa, such as Shigella, Clostridium, and Escherichia, which produce alpha-toxins and are linked to necrotizing enterocolitis, were found in layer chicks exposed to heat. Conversely, beneficial bacteria were rare, including Lactobacillus and Ruminococcaceae (Heida et al., 2016). Because the metabolites of bacteria in the genus Lactobacillus can control the acid-base equilibrium in the intestine, promoting the growth of a healthy but non-pathogenic microbiome, these bacteria are frequently utilized as probiotics (Menconi et al., 2011). Additionally, under heat stress, several species in the Lachnospiraceae group are suppressed (Biddle et al., 2013; Meehan and Beiko, 2014). These species generate a comparatively high amount of butyrate, which promotes intestinal epithelium growth and aids in intestinal health maintenance. Although it is the main energy source for colonocytes in the large intestine and is known to affect gene expression by acting as a histone deacetylase (HDAC) inhibitor and to affect signaling by activating several G-protein-coupled receptors, butyrate is generally less abundant than other SCFA (60% acetate, 25% propionate, and 15% butyrate; at least in humans) (Liu et al., 2018). Numerous studies have shown that butyrate is helpful in reducing inflammation and preserving the integrity of the intestinal barrier (Liu et al., 2018). Thus, through the effects of butyrate signaling on the peripheral and central nervous systems, variations in the quantity of butyrate-producing bacteria could modulate the MGBA (Liu et al., 2018).

Heat Stress Reduces Intestinal Integrity

In healthy conditions, the habitat of the gut microbiota is usually steady. In order to survive and produce metabolites that increase host intestinal immunity and inhibit the growth of pathogens, commensal bacteria compete with pathogenic bacteria for space and nutrients found in the intestine. This process protects the gut epithelium. Stressful events, however, can simultaneously damage gut barrier integrity and change the microbiome (Tannock and Savage, 1974; Söderholm et al., 2002; MacDonald, 2005). Intestinal pathogens can cause diseases and reduce the effectiveness of food digestion and assimilation if they have breached the mucosal layer and gained access to the host circulation (Sansonetti, 2004; Keita and Söderholm, 2010).

There is proof that the intestinal mucosa, which is prone to inflammation and injury from microbiota changes as well as heat stress, can occasionally adapt to optimize nutrient absorption. In addition to a damaged mucosal layer in the jejunum and decreased plasma

thyroid hormone and increased plasma corticosterone, heat-treated chicks also showed enhanced glucose transport across the jejunal epithelium, which may have made up for their decreased food intake and consequent lack of energy (Garriga et al., 2006). However, in a different study, the chicks' intestinal systems suffered considerable damage when they were exposed to a temperature of 35°C, which was 5 degrees higher. They also had lower villus heights and functional absorptive surface areas, as well as greater blood endotoxin levels. These negative effects were not mitigated by host adaptations alone; instead, exogenous butyrate supply was necessary to reduce symptoms, indicating yet another way that butyrate is important for preserving intestinal structure and function (Abdelqader et al., 2017).

Due to its proximity to the cecum and its ability to receive digestive end products that are not absorbed in the proximal small intestine, the ileum is a special type of intestinal niche. Compared to the proximal small intestine, it is home to more bacteria, including the pathogenic Salmonella, and offers a rich source of food substrate for fermentative activity (Fanelli et al., 1971). The first line of defense against invasive germs is the gut (Fagarasan, 2006). A systemic infection can result from Salmonella adhering at compromised sites and translocating into the host if the chicken small intestine epithelium is compromised for any cause (Burkholder et al., 2008). This was noted in hens who experienced either starvation or heat stress for a full day (McHan et al., 1988; Alhenaky et al., 2017). When chicks are exposed to high temperatures either abruptly or chronically, Salmonella invades and is subsequently found in the muscles, spleen, and liver. These foreign pathogens are usually cleared by the liver and spleen after being taken up by macrophages and circulated. But it's still unknown which organs Salmonella preferentially targets during a systemic infection (Chappell et al., 2009).

The impact of heat stress on the intestinal epithelium is mediated by two different pathways, according to theories. The first is that high ambient temperatures and increased oxidative activity cause reactive oxygen and/or nitrogen species to be formed, overriding the ability of endogenous antioxidant mechanisms (Hall et al., 2001). These free radical molecules are produced when chicks are exposed to heat, which damages the epithelial cell membranes and reduces the expression of TJ genes and the number of tight junctions (TJ). As a result, the gut barrier opens up to bacterial endotoxins' paracellular invasion. The second mechanism is that proinflammatory cytokines, which also cause damage to the TJ, are produced in response to heat stress (Al-Sadi et al., 2010). Among these cytokines, the concentrations in the bloodstream of interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α) are raised in chicks under heat stress. T cells generate IL-2, which when released, stimulates other cell types like macrophages, which release proinflammatory cytokines like TNF-α to cause inflammation (Hoyer et al., 2008). Nevertheless, endotoxins may also increase the release of IL-2 (Costalonga and Zell, 2007); Consequently, this process could have an indirect or secondary effect.

Heat Stress Activates the HPA Axis

An organism's response to internal and/or external stressors is integrated and mediated by the HPA axis, a vital mechanism (McEwen, 2000). In rodents and birds, its activation is characterized by the release of ACTH, the activation of hypothalamic CRF, and the synthesis of corticosterone (Iyasere et al., 2017). The HPA axis is triggered by both acute and chronic exposure to high ambient temperatures and is often characterized by raised blood cortisol levels in the animal. Increases in the amount of corticosterone in the blood are linked to a variety of physiological reactions, including abnormal immunological and inflammatory responses, reduced food intake and growth performance, and more (Quinteiro-Filho et al., 2012a; Beckford et al., 2020).

Activation of the HPA axis results in the production of numerous additional hormones, neuroactive substances, and cytokines in addition to corticosterone. Numerous bodily systems, including the immunological, endocrine, and central nervous systems, share these components, which directionally mediate systematic interplay by ligand binding to receptors (Kaiser et al., 2009). For instance, the HPA axis and sympathetic outflow are the main ways in which the CNS controls immunity (Ziegler, 2002). Catecholamines from sympathetic activity and corticosterone from the HPA axis are the hormones involved in control. The production of inflammatory cytokines may be further regulated by the two main catecholamines norepinephrine (NE) and epinephrine (E), which have been shown to increase the expression of anti-inflammatory IL-10 and transforming growth factor β and decrease proinflammatory IL-12, TNF-α, and interferon γ (Johnson et al., 2005). Parasympathetic influx can then either pick up or send signals from visceral organs or tissues—especially the GIT—back to the HPA axis (Calefi et al., 2016). In fact, gut inflammation feeds back to the HPA axis, which controls the immune system's response against invaders (Karrow, 2006).

Even though gut immunity and inflammation are associated with heat stress induced HPA axis activation (Lara and Rostagno, 2013; Galley and Bailey, 2014; Scanes, 2016; Calefi et al., 2017), Few have even ventured to look into actual alterations in brain activity and gut microbiota. Because of compromised intestinal integrity and function as well as increased permeability, pathogenic species like Salmonella and Escherichia coli thrived in heat-stressed mice, but beneficial commensal bacteria were often less competitive (Song et al., 2013). In a study involving broiler chickens, changes in the concentrations of monoamines in key brain regions, such as a decrease in 5-HT, NE, and E in the hypothalamus and dopamine in the midbrain, were caused by heat stress and/or intestinal infection with Clostridium and Eimeria spp., which are protozoal and bacterial species, respectively (Calefi et al., 2019). According to the authors' conjecture, the data showed that intestinal immune cells' enhanced production of cytokines in response to the pathogen challenge activated the HPA axis. That study did not look at monoamine concentrations or the production of cytokines in the small intestine. Future studies should concentrate further on the relationship between neurobiology and the gut microbiota in intestinal dysfunction models generated by heat and pathogens.

Alleviating the Adverse Effects of Heat Stress

Many approaches, ranging from better housing management to nutritional interventions including changing the macronutrient composition and adding prebiotics, probiotics, and their combination, known as synbiotics, have been used to reduce heat stress in hens (Lara and Rostagno, 2013).

Probiotics are typically the predominant beneficial bacteria in the gastrointestinal tract (GIT), including live yeasts, Lactobacillus, and Bifidobacterium. By guaranteeing their continuous establishment and proliferation, exogenous supplementation helps maintain a healthy gut. This, in turn, influences the HPA axis and chicken behavior or physiology through immunomodulation, metabolic homeostasis, and neuroendocrine loops (Wang et al., 2018). Usually, the host's commensal bacteria are the most potent probiotics (Dogi and Perdigón, 2006). For instance, when added to the broiler meal, Bacillus subtilis fought for resources and colonizing sites with pathogens like Clostridium perfringens and Eimeria spp., preventing their invasion and colonization of the gut (Lee et al., 2015). By enhancing microbiota variety and encouraging the growth of the advantageous Lactobacillus, B. subtilis has been shown to prevent bacterial pathogenic reproduction and enhance feed utilization (Knap et al., 2011). Furthermore, when persistent heat stress suppresses the activity of intestinal digestive enzymes, B. subtilis can promote the release of those enzymes to speed up nutrition digestion (Chen et al., 2009). Probiotic-supplemented hens showed longer villi and greater surface areas, which shielded the bird against heat-induced gastrointestinal dysfunction (Deng et al., 2012; Song et al., 2014).

Prebiotics are generally understood to be food elements, most commonly saccharides, that help the host by promoting the growth of specific bacterial species that use them as fermentative substrates but are not digested (or absorbed) by the host. Fructo-oligosaccharides (FOS), mannan-oligosaccharides (MOS), and inulin are typical examples. Harvested from the yeast cell wall, mannan-oligosaccharide is one of the most widely utilized prebiotics in the chicken business. Synbiotics are probiotics and prebiotics combined in a way that works well (Schrezenmeir and de Vrese, 2001). When added to food, prebiotics, and probiotics both have positive benefits on an animal's health (Sohail et al., 2012; Sugiharto et al., 2017; Awad et al., 2021). Nevertheless, when taken together as synbiotics, they might have additive and synergistic effects. In addition to promoting the colonization and growth of commensal microbes, synbiotics also mediate systemic and local activities by activating signaling in the microbiome-gut-brain and microbiome-gut-immune axes. These further impacts host physiology and behavior (Rooks and Garrett, 2016). In one study, broilers were subjected to either normal or high temperatures and fed either a regular diet or a diet supplemented with synbiotics. Synbiotic administration was linked to increased preening, decreased panting, and wing lifting in addition to attenuating heat stress-induced anorexia and body weight loss (Mohammed et al., 2018). Depending on their composition, synbiotics can have different impacts on the gut microbiome due to the wide range of probiotic species and prebiotic saccharides that they include. For example, distinct

commensal microorganisms were preferentially encouraged when MOS, but not FOS, was added to a synbiotic combination. Additionally, MOS was linked to the binding and removal of harmful bacteria from the gastrointestinal tract (Spring et al., 2000; Sohail et al., 2012).

Conclusion and Implications

In conclusion, heat stress causes several physiological changes that either directly or indirectly control the ecology of gut microbes. These modifications result in altered nutritional and environmental conditions within the gut, which compromise the integrity of the intestinal epithelium or barrier and cause inflammatory states as well as activation of the autonomic nervous system and HPA axis. There are still many unknowns, despite mounting evidence linking heat stress to modifications in the gut and host brain (such as changes in monoamine concentrations) that are impacted by changes in the intestinal microbiota. For instance, most studies examined the relationship between heat stress and the gut microbiota of chickens, but few verified the precise compositional changes of microbiota in response to various probiotic and prebiotic interventions or under various heat stress conditions (e.g., acute, chronic, one-time, or repetitive) in chickens of different types, breeds, and ages. Additionally, diverse metabolites (like SCFAs) and neuroactive molecules (like 5-HT) produced by the gut microbiota under varied heat stress situations need to be considered and investigated further. To enhance chicken performance while exposed to heat and to ascertain the impacts on microbiome composition, future research should concentrate on utilizing more combinations of probiotics and prebiotics. Although the effects of heat stress on host and microbial physiology are well established, it is not evident how much the former drives the latter and vice versa. Therefore, understanding how the host and microbial cells interact to drive physiology and behavior, as well as the mechanisms that change the physiology of the GIT and microbiome, will enable comprehensive solutions to lessen the consequences of heat stress in both humans and animals.

Author Contributions

The review's concept was created by T.K, A.F, and S.A. T.K. M.S.A, I.A, and A.H wrote the manuscript's draft. The manuscript was edited by T.K, A.F, and S.A. The final draft was read and approved by all authors.

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Conflict of Interest

The research was carried out without any financial or commercial ties that might be seen as having a conflict of interest, the authors disclose.

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