



Review Article

Microbiota-gut-brain axis and nutritional strategy under heat stress

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ABSTRACT

Heat stress is a very universal stress event in recent years. Various lines of evidence in the past literatures indicate that gut microbiota composition is susceptible to variable temperature. A varied microbiota is necessary for optimal regulation of host signaling pathways and disrupting microbiota-host homeostasis that induces disease pathology. The microbiota-gut-brain axis involves an interactive mode of communication between the microbes colonizing the gut and brain function. This review summarizes the effects of heat stress on intestinal function and microbiota-gut-brain axis. Heat stress negatively affects intestinal immunity and barrier functions. Microbiota-gut-brain axis is involved in the homeostasis of the gut microbiota, at the same time, heat stress affects the metabolites of microbiota which could alter the function of microbiota-gut-brain axis. We aim to bridge the evidence that the microbiota is adapted to survive and thrive in an extreme environment. Additionally, nutritional strategies for alleviating intestinal heat stress are introduced.

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1. Introduction

Heat stress is one of the most vital environmental stressors challenging human and animal health (Rojas-Downing et al., 2017). All animals have a thermal comfort zone which is essential in the upkeep of physiological functions. However, under conditions when the increasing temperature is beyond the upper critical temperature of the range, the animals begin to suffer heat stress (Rojas-Downing et al., 2017). The molecular mechanisms that sense and control temperature fluctuations are complex. Fortunately, animals have developed phenotypic responses to heat acclimation,

such as decreased feed intake and altered physiological functions (Horowitz, 2001; Nardone et al., 2010). The relative percentages of *Candidatus Arthromitus* sp. *SFB-mouse-japan* and *Lactobacillus murinus* were significantly reduced and some anti-inflammatory component such as salicin were increased in cecum after heat stress (Wen et al., 2021). The plastic entity of the intestinal microbiota guarantees a rapid adaptation of the host in response to environmental changes (Candela et al., 2012). The survival of microbes and organisms is the result of contending with environmental perturbations and fluctuations, especially severe environmental temperature changes (Shapiro and Cowen, 2012). Moreover, a higher temperature could speed up the growth of pathogens that live part of their life outside of their host, which negatively affects the health of livestock (Harvell et al., 2002; Rojas-Downing et al., 2017). Therefore, an appropriate intestine function is a central component in counteracting the negative consequences of heat stress (Table 1, Fig. 1).

The gastrointestinal microbiota plays an essential role in the immune system, stress response, and energy regulation (Chevalier et al., 2015; Nieuwdorp et al., 2014; Ubada and Pamer, 2012). Imbalanced microbiota promotes the development of diseases

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Table 1
Reported changes in intestine microbiota under heat stress.

Animal	Age/body weight	Heat treat	Microbiota (heat stress vs. room temperature)	Location	Reference
Broilers	28 d old	31 ± 1 °C	<i>Streptophyta, Faecalibacterium, Rothia, Alistipes, Azospirillum, and Oscillibacter</i> decreased	Ileal	Wang et al. (2018a,b)
Cobb male broilers	21 d old	33 ± 1 °C 10 h/d for 21 d	<i>Lactobacillus</i> and <i>Bifidobacterium</i> decreased; <i>Salmonella, Escherichia coli, and Clostridium</i> increased	Mid-jejunum	Zhang et al. (2017)
Dairy cows	3.06 ± 1.1 years	27.63 ± 5.34 °C	<i>Peptostreptococcaceae, Turicibacter, and Clostridium-sensu-stricto</i> increased; <i>Ruminococcaceae-UCG-005, Rikenellaceae-RC9-gut group, Bacteroides</i> decreased	Feces	Li et al. (2020)
Grow-finishing pigs	30 ± 1 kg body weight	35 ± 1 °C for 24 h	Proteobacteria increased; Bacteroidetes decreased	Feces	Xiong et al. (2019)
Large white × créole pigs	23 weeks	3 weeks at 29 °C	Firmicutes, Spirochaetes, Fibrobacters increased; Bacteroidetes decreased	Feces	Sciellour et al. (2019)
Laying hens	340 d of age	29.6 to 34.1 °C 6 to 8 h/d for 46 d	Firmicutes increased; Bacteroidetes increased (phyla)	Feces	Zhu et al. (2019)
Primiparous sow	Day 107 of gestation	28 to 32 °C for 24 d	<i>Clostridiales</i> and <i>Halomonas</i> increased; <i>Bacteroidales</i> and <i>Streptococcus</i> decreased	Feces	He et al. (2019a)
Ross male broilers	21 d old	33 °C for 10 h for 21 d	<i>Clostridium</i> increased; <i>Lactobacillus</i> and <i>Bifidobacterium</i> decreased	Distal of duodenum to ileocecal junction	Song et al. (2014)

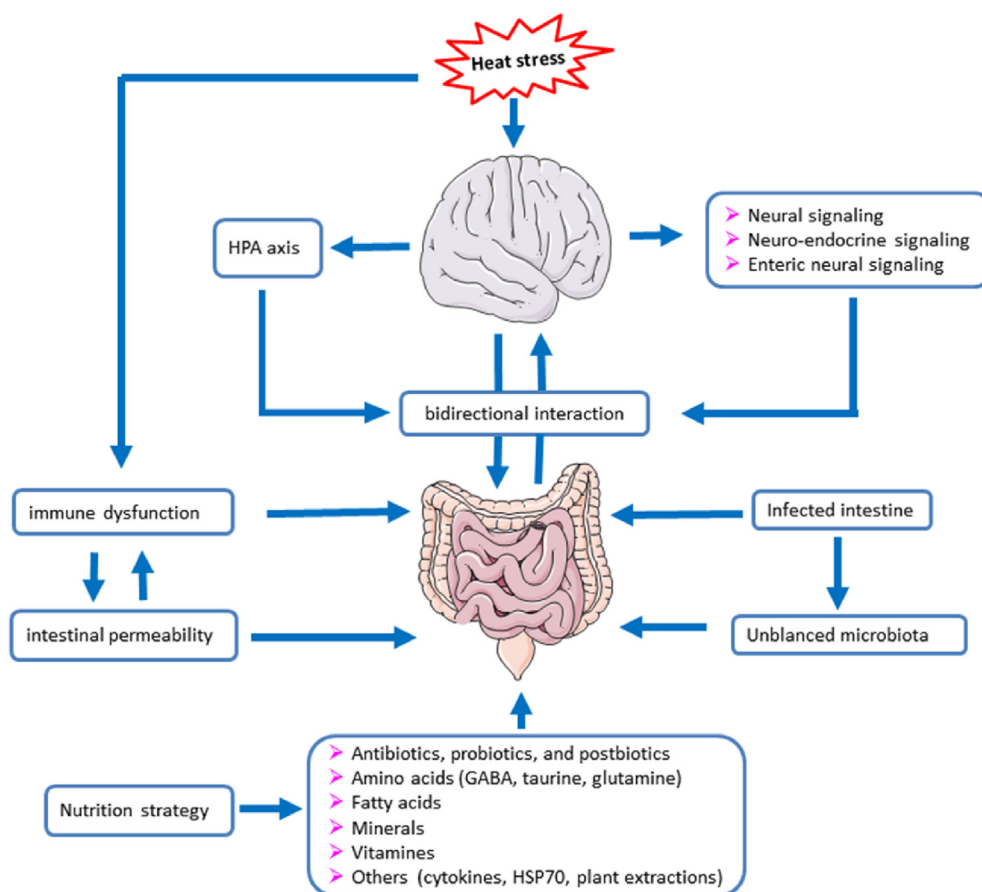


Fig. 1. The microbiota–gut–brain axis contains bidirectional communication, through several pathways, between the gut and the brain, and the nutrition strategy to alleviate heat stress. HPA = hypothalamic–pituitary–adrenal; GABA = gamma amino butyric acid; HSP70 = heat shock protein 70. During heat stress, changes at the level of the central nervous system can affect intestine permeability and microbiota composition. In turn, dysbiosis may contribute to prolonged dysfunction and microbial metabolism imbalance, further disturbing gut–brain communication. Nutrition strategies has been developed to alleviate heat stress.

(Sobhani et al., 2019). Many factors contribute to shaping the microbiota composition, including environmental factors, diet, and disease (Hand et al., 2016; Sonnenburg et al., 2016). Microbiota perturbations by temperature exert a modulatory effect on adult animals through the endocrine and neuroendocrine pathways, which may be involved in gut microbiota-to-brain signaling (Vijay-Kumar et al., 2010). Meanwhile, some small molecules produced by microbiota could alter many important physiological processes (Albenberg and Wu, 2014). However, the mechanical response to cellular stress remains unclear. In this review, we summarized the negative effect of heat stress on human and animal health, the regulatory response and nutritional strategies to alleviate the thermometric stress.

2. The negative effect of heat stress on human and animal health

2.1. Effects of heat stress on intestinal function

To deal with the harmful effects of environmental stress, all living organisms, including host and microbiota, have evolved rapid molecular responses to fix the damage and protect against further exposure to that condition (Estruch, 2000). Positive and negative feedbacks are performed to maintain environmental and compositional homeostasis, and these feedbacks are expected to control the interaction between the microbial metabolic activities and host pathways (Lozupone et al., 2012).

2.1.1. Immunity

The microbiota has been recognized as contributing to inflammatory immune responses (Blander et al., 2017; Zong et al., 2020). Heat stress activates the immune response and disrupts the homeostatic relationship between the microorganism and the host, resulting in the gut being susceptible to invasive pathogen infection. The immune system interacts with nerves and endocrine systems by reacting to several stressors which affect cell-mediated immune actions.

The effect of heat stress on immune function are varied in response to acute and chronic heat stress. Acute heat stress decreases the number of T helper cells and increases the number of natural killer (NK) cells (Nagai and Iriki, 2001), which may reduce immune function. Chronic thermal exposure induces a decrease in the number of type 1 T helper cells and an increase in the number of type 2 T helper cells. Inequity between type 1 T helper cells and type 2 T helper cells may cause concomitant changes in cytokine release (Nagai and Iriki, 2001). The number of CD8 T cells was significantly increased and the ratio of CD4 to CD8 T cells was reduced in heat-stressed pigs (Gu et al., 2012). After a long-term heat challenge (>24 h), the number of infiltrating cells (macrophage-like phenotype) was increased in the mucosa and submucosa jejunum of cows, and bacterial compounds may trigger a modulated immune repertoire to keep balance between commensal bacteria and the immune system of jejunum (Koch et al., 2019). Under chronic heat stress, the proteins (such as heat shock protein family A member 8) involved in immune defense are increased (Cui et al., 2016). Taking these together, the immune function tends to be weak under acute heat stress, while improved under chronic heat stress.

Upon heat shock, mammalian cells harmonize rapid, dynamic, and extensive changes in transcription that are mainly modulated at pause release (Mahat et al., 2016). The transcription factors activating protein-1 (AP-1), an important mediator to regulate the transcription of genes related to immune regulation, is activated in the intestine of rats exposed to heat stress, suggesting an increased

immune response to defend against heat stress (Zhang et al., 2015). Heat stress could induce inflammation response and then cause tissue damage, including intestine and muscle. In an experimental baboon model, heat stress quickly stimulated the simultaneous release of anti-inflammatory cytokines (interleukin [IL]-10, IL-1 α , and IL-8) in plasma (Bouchama et al., 2005; Hall et al., 2001; Ji et al., 2014; Reber et al., 2016). Elevated intestinal IL-6, tumor necrosis factor (TNF)- α , and IL-1 β levels increased intestinal cell permeability by increasing claudin, occludin, and zonula occludens 1 protein expression (Robinson et al., 2015; Song et al., 2017). Additionally, the activated mitogen-activated protein kinase and nuclear factor kappa-B (NF- κ B) signaling pathway and AP-1 signaling pathway contribute to semitendinosus muscle and intestinal injury under heat stress (He et al., 2015; Ganesan et al., 2017). Heat shock proteins, a kind of proteins produced under heat stress by cells, modulate the effects of inflammatory cascades, resulting in the endogenous generation of reactive oxygen species by inhibiting pro-inflammatory factors (Ikwegbue et al., 2017). These results suggested that organisms launch inflammation responses to heat stress.

2.1.2. Intestinal barrier functions

The thermal environment is the main factor that triggers the negative effects to humans and animals. Heat stress harms the intestinal function of digestion and absorption. The intestinal epithelium undertakes rapid and perpetual renewal in humans and animals (Alonso and Yilmaz, 2018), which is crucial for nutrient digestion and absorption. However, under heat stress condition, the feed intake and feed efficiency were decreased (Bartlett and Smith, 2003). Mechanistically, heat stress remarkably downregulates the mRNA expression of cholecystokinin in the duodenum and jejunum (Song et al., 2012). Correlation analysis have found that high cyclic temperature had significant effects on the composition and structure of cecal microbiota which was mainly related with decreased feed intake in laying hens (Xing et al., 2019). Moreover, a higher feed efficiency characteristically showed a more abundant and diverse microbiome (Zhang et al., 2021). Meanwhile, heat stress decreased the digestive and absorptive capacity by shortening the villi length and reducing the number of goblet cells in the duodenal jejunal epithelium (Liu et al., 2012). Interestingly, the susceptibility to heat stress is varied in the chicken intestine, with the ileum showing a more pronounced response after heat stress exposure than the jejunum (Varasteh et al., 2015a). The most severe morphological change occurs 3 d after exposure to heat stress (40 °C for 5 h each day) (Yu et al., 2010), which is associated with downregulation of the epithelial growth factor signaling of the jejunum. However, the pig intestinal epithelial tissue only starts to regrow within 6 d during the initial recovery (Liu et al., 2009), which further worsens the rebuild of intestine.

Heat stress causes an injury to the intestinal mucosa. When exposed to heat stress, the intestinal mucosa increases the capacity to absorb sugars which is entirely dependent on the adaptations of apical glucose transporter 1 expression (Garriga et al., 2006). Similarly, intestinal glucose transport and blood glucose are increased under heat stress, while the expression of glucose transporter 2 is elevated in the ileum of growing pigs (Pearce et al., 2013). Adversely, the expression of glucose transporter 2 and fatty acid-binding protein 1 (FABP1) was significantly decreased in jejunum of broiler chicken. Interestingly, the plasma glucose and very low-density lipoprotein did not significantly alter (Sun et al., 2015). It is suggested that animals could cope with energetic and anabolic demands at high ambient temperatures.

2.2. Effects of heat stress on microbiota–gut–brain axis

The microbiota has been recognized as contributing to stress responses (Sekirov et al., 2010). Bidirectional intestine–brain interactions regulate gut function in health and diseases, and the enteric flora (commensal and pathogenic organisms) play an important role in these interactions. Through the hypothalamic–pituitary axis, the autonomic nervous system, and the brain affects the environment of the intestinal microbiota indirectly and directly (Fan et al., 2020; Ma et al., 2020).

2.2.1. Microbiota homeostasis

The microbial community, including the population, composition and function of microbiota, is causally linked with heat tolerance (Lokmer and Mathias, 2015; Ziegler et al., 2017). Heat stress had no remarkable effect on alpha diversity but affected the main phyla and genera of the goat rumen microbiota (Zhong et al., 2019). After 14 d of heat stress treatment, opportunistic pathogens such as *Campylobacteriales*, *Veillonellaceae*, and *Megasphaera* substantially increase (Hu et al., 2020). On the other hand, we also found some probiotics, such as segmented filamentous bacteria and *L. murinus*, were diminished in heat stressed mice (Wen et al., 2021). After applying fecal microbiota transplantation from heat-stressed pigs to mice, it was found that *Bacteroides* was significantly reduced while *Akkermansia* was significantly augmented (Hu et al., 2020). These results suggested that the heat stressed subjects might be enriched with microbiome with therapeutic properties. Although it seems a contradictory description which maybe related to the process of heat stress, a previous study has found that the feces of animals with disease and patients contains the benefit microbiota to alleviate disease (Liu et al., 2019). The high temperature environment alters microbiota metabolism. The ambient environment mainly affects the homeostasis of carbohydrates, lipids, and amino acid metabolism in microbiota (Chen et al., 2018; Cui et al., 2019; Tian et al., 2015; Wen et al., 2021; Zhong et al., 2019; Zhu et al., 2019), resulting in a higher expression of the environmental adaptation signaling pathway and immune-related pathway (Chen et al., 2018). Different microbiota in spring and summer were mainly concentrated in the functions associated with infectious diseases, immune system diseases, and lipid metabolism in dairy cows (Li et al., 2020).

2.2.2. Microbiota–gut–brain axis

Gut microbial metabolism is informally conjoined with host health and diseases. The microbiota can produce many neurotransmitters and neuromodulators that regulate the signal transduction of the host. It has been shown that *Lactobacillus* spp. and *Bifidobacterium* spp. generate gamma amino butyric acid (GABA), *Escherichia* spp. and *Saccharomyces* spp. generate noradrenalin, *Bacillus* spp. produces dopamine, and *Lactobacillus* spp. generates acetylcholine (Barrett et al., 2012; Duszka and Wahli, 2018; Lyte, 2011). The metabolites of aromatic amino acids are converted by the gut microbiota, and they can regulate intestinal epithelial cell homeostasis, immune, metabolic, and neuronal responses (Liu et al., 2020). The neurotransmitters produced by the microbiota in the gut lumen may stimulate epithelial cells to release molecules that in turn induce neural signaling within the enteric nervous system, or act directly on primary afferent axons (Forsythe and Kunze, 2013).

The microbiota–gut–brain axis is a well-known mechanism that could regulate intestinal function. The disruption of the gut–brain axis may be involved in acute and chronic intestinal diseases (Mayer et al., 2014; Rhee et al., 2009). The effects of the intestine microbiota result in changes in the blood levels of pro-inflammatory and anti-inflammatory cytokines that directly affect

brain function (Cryan and Dinan, 2012). The brain affects commensal flora directly or indirectly, through changing gastrointestinal motility and secretion, and intestinal permeability by secreting signal molecules into the intestinal lumen (Mayer et al., 2014; Rhee et al., 2009). Communication from the enteric microbiota to the host can be achieved via a complex mechanism, including epithelial cell, receptor-mediated signaling. In *Salmonella typhimurium* infection, enteric neurons produce IL-18, which is required for antimicrobial protein production in homeostatic goblet cells (Jarret et al., 2020). Long-term heat stressors activate the hypothalamic–pituitary–adrenal axis, inducing the serum parameter changes, and increasing the concentrations of TNF- α , heat shock protein 70 (HSP70), LPS, and corticosterone (Quinteiro-Filho et al., 2012; Zhu et al., 2019). The increase of corticosterone could have deleterious effects on the microbiota composition alterations, activation of the neuroimmune response (Amini-Khoei et al., 2019), causing an increment of gastrointestinal permeability (de Punder and Pruimboom, 2015). It has been suggested that the metabolites of pathogenic bacteria are increased, an immune response is triggered, and the organism is adaptively regulated in response to heat stress (He et al., 2019a).

The central nervous system, the enteric nervous system, and the neuro-endocrine pathways are all related to communication with the intestine microbes (Cryan and Dinan, 2012). Studies have shown that the communication between the microbiota and brain involves the vagus nerve, which transmits information from the intestinal environment to the central nervous system. Recently, researchers have found synapses in the enteroendocrine cells, which are gut sensory epithelial cells. The cells with synapses are called neuropod cells. They play a central role in transducing sensory signals from the gut milieu in the intestine to the brain through fast neurotransmission to neurons, including those of the vagus nerve (Kaelberer et al., 2020).

Heat stress increases the risk of enteric bacterial pathogens. Enteric neurons express IL-18, which can directly kill the enteric bacterial pathogens via antimicrobial peptides expressed by goblet cells (Jarret et al., 2020). However, bacteria growing in mucosal biofilms are less affected by environmental changes, such as alterations of the intestinal transit rate and luminal contents in response to antibiotics than unattached organisms. It is difficult to modify the structure and composition of these communities (Macfarlane and Dillon, 2007). Lai et al. (2019) has found that nociceptors shape the gut microbiota including the segments filamentous bacteria levels to resist *Salmonella* infection by suppressing M cell density and releasing calcitonin gene-related peptides to mediate segments filamentous bacteria colonization and limit bacterial invasion.

Temperature fluctuations exert a modulatory effect on some of these measures in adult animals, including the endocrine and neurocrine pathways, which may be involved in gut microbiota-to-brain signaling. Hyperthermia induces the secretion of pro-inflammatory cytokines, such as IL-6 and interferon γ (Leon and Helwig, 2010). Recently, various lines of evidence have shown that IL-6 concentrations are correlated with stressor-induced alterations in the levels of 3 bacterial genera: *Coprococcus* spp., *Pseudobutyrvibrio* spp., and *Dorea* spp. (Bailey et al., 2011). The increased colonization of *Rodentium* is correlated with the mRNA expression of TNF- α in the colon, and disruption of the composition of the microbiota increases the pathogen colonization (Bailey et al., 2010).

3. Nutrition strategy

Diet is the primary modulator of gut microbiota composition, and the nutrient-microbiome-host interplay provides us with an

overarching framework to determine the function of the gut-brain axis (Ezra-Nevo et al., 2020). Heat stress response noticeably alters postabsorptive carbohydrate, lipid, and protein metabolism independently of a reduced feed intake through coordinating changes in the fuel supply and its utilization by several tissues (Baumgard and Rhoads, 2013). Therefore, nutrition strategies to reduce heat stress must be developed to maintain human and animals health.

3.1. Antibiotics, probiotics, and postbiotics

Supplementation with antibiotics, probiotics, or postbiotic can modulate the intestinal microbiota in heat conditions. During summer (23 to 34 °C, relative humidity 65% to 89%), supplementation with avoparcin, flavomycin, zinc bacitracin, or probiotics (Bospro, Lacto-Sacc) had a beneficial effect on physiological status, including thermoregulation (Abdel-Samee, 2010). The positive effect of probiotics is beyond antibiotics. For chicks exposed to heat stress (36 ± 1 °C for 3 h daily) for 3 weeks, supplementation with 1 g/kg lactobacillus culture in the diet promoted the growth performance more than that with 50 mg/kg oxytetracycline (Zulkifli et al., 2000).

The potential benefits of probiotics against heat stress in poultry have been discussed (Sugiharto et al., 2017). In irritable bowel syndrome patients, supplementation with *Lactobacillus gasseri* CP2305 attenuates the reduction of *Bifidobacterium* spp. and the elevation of *Streptococcus* spp. (Nishida et al., 2019). Pretreatment with the *Bacilli subtilis* BSB3 strain twice a day for 2 d can prevent the complications of heat stress (45 °C, relative humidity 55% for 25 min), such as morphological changes (villus height and total mucosal thickness) of the intestine, and bacterial translocation (Moore et al., 2014). Mixing 1×10^6 CFU/g *Bacillus subtilis* into the diet can effectively ameliorate heat-induced inflammatory reactions by regulating microbiota-modulated immunity (Wang et al., 2018a,b). A mixture of 2 *Lactobacillus* strains improved the bacterial population of the broiler cecal contents by increasing good flora and decreasing the *Escherichia coli* population under high ambient temperature conditions (Faseleh Jahromi et al., 2016). These indicated that probiotics are good potential candidates to alleviate heat stress.

Postbiotics refer to soluble metabolic products or byproducts, secreted by live bacteria, or released after bacterial lysis, and they have been widely used for their various signaling molecules which may have anti-inflammatory, immunomodulatory, and antioxidant activities (Aguilar-Toalá et al., 2018). Oral treatment with *Saccharomyces cerevisiae* fermented prebiotic for 14 d before exposure to heat stress prevents the adverse effects of heat stress by elevating gut beneficial bacteria, mostly butyrate-producing bacteria (Ducray et al., 2019). Similarly, pretreatment with galacto-oligosaccharides before heat stress exposure (40 to 42 °C) for 24 h partly prevented the heat-induced injury of the monolayer integrity in human epithelial colorectal adenocarcinoma cells (Varasteh et al., 2015b). *S. cerevisiae* and *Lactobacillus acidophilus* fermentation products protect the jejunum mucosa against heat stress-induced injury in pigs (Kumar et al., 2017). The supplementation of 0.3% postbiotics (produced by *Lactobacillus lantorum*) has a positive effect on the gut microbiota, with higher populations of caecum total bacteria and *Lactobacillus* and lower populations of *Salmonella*, *Enterobacteriaceae*, and *E. coli* (Humam et al., 2019). Postbiotics seem to not function in whole intestinal segments, as dietary galacto-oligosaccharides only avert the heat stress-related changes in the jejunum (Varasteh et al., 2015a,b).

Antibiotics, probiotics, and postbiotics can alleviate heat stress, and microbiota are involved in this effect. However, the mechanism is complex and needs further investigation.

3.2. Amino acids

Amino acids nutrition is vital for the health of the host and microbiota, especially in heat conditions. Supplementation with 100 mg/kg GABA improved the immune response and performance traits of broilers exposed to cyclic heat stress (Chand et al., 2016). Mechanismly, the GABA-ergic system shapes the activation and function of immune cells and improves intestinal IL-17 expression by activating the mechanistic target of rapamycin complex 1-ribosomal protein S6 kinase 1 signaling (Ren et al., 2016, 2019). Under stress conditions, body usually exhibited taurine deficiency (Wen et al., 2019a). Therefore, it is essential to supplement taurine in diet. Taurine shows beneficial effects on stress alleviation, which could reduce the level of reactive oxygen species, and protect mitochondria from oxidative attack (Lu et al., 2019; Wen et al., 2019b, 2020a, 2020b). This may indicate a recognition site specific for taurine, accountable for its effects on thermoregulation (Frosini et al., 2003). Glutamine exhibits the ability to attenuate hyperthermia (Soares et al., 2014). The advantageous effects of glutamine on intestine nutrition and health are related to amino acid metabolism in the intestinal microbiota (Dai et al., 2013; Ren et al., 2014). Glutamine stimulates the growth of intestinal mucosa, protecting the intestine from injury under various stress conditions (Wang et al., 2015), and partially alleviating the adverse effects of heat stress on intestinal barrier function in broilers through promoting epithelial cell proliferation and renewal, amending the function of intestinal mucosa barrier, and controlling the secretion of cytokines (IL-10 and TNF- α) (Wu et al., 2021). In addition, glutamine enhances the cell-mediated immune response which is weakened in cows during the summer season (Caroprese et al., 2013). Many studies have found that glutamine can strengthen stress-induced heat shock protein expression in vitro and enhance cell survival against various stressful stimuli (Wischemeyer, 2002). When glutamine was reduced (from 0.5 to 0.125 mmol/L, a physiological level to a pathological level) during the stress response, the expression of *HSP70* decreased by 40% (Oehler et al., 2002). These results suggested that extra amino acid supplementation had a potential to reduce heat stress.

3.3. Fatty acids

Fatty-acid metabolism regulates heat resistance. N-3 polyunsaturated fatty acids exert an effect on maintaining and protecting the tight junction. Preincubation with eicosapentaenoic acid effectively attenuates the decrease in transepithelial electrical resistance and the impairment of intestinal permeability induced by heat exposure. Additionally, the distortion and redistribution of tight junction proteins and their damaged morphology are effectively prevented by pretreatment with eicosapentaenoic acid (Xiao et al., 2013). Ferulic acid protects against heat stress-induced intestinal epithelial barrier dysfunction by activating the phosphatidylinositol 3-kinase/protein kinase B mediated nuclear factor erythroid-2-related actor 2/heme oxygenase 1 signaling in intestinal epithelial cells (He et al., 2019b).

Short-chain fatty acids (SCFA) represent the major carbon flux from the diet through the intestinal microbiota to the host, and play an important role in maintaining the homeostasis of the hosts' health and disease. Heat stress exerts a negative effect on intestinal microbiota and their SCFA metabolites. When grow-finishing pigs and primiparous sows during late gestation are exposed to heat stress, their metabolic activities changes, decreasing the contents of propionate, butyrate, and total SCFA in their feces (He et al., 2019a; Xiong et al., 2019), while increasing that of azelaic acid (He et al., 2019a). The contents of nonesterified fatty acids (myristic acid, palmitic acid, and linoleic acid) and SCFA (3-hydroxybutyric acid

and maleic acid) increased, which was an adaptive reaction to a negative energy balance (Cui et al., 2019). Correlation analysis between significant microbes and metabolites indicated that heat stress-induced microbes alterations are likely to cause the shifts in the intestinal metabolism (He et al., 2019a).

3.4. Minerals

Minerals play an important role in heat conditions. The forms of mineral have a varied effect on alleviate heat stress. Oral consumption of the organic form of minerals is superior to the inorganic form to alleviate heat stress. In acute heat stress, organic zinc is superior to sulfate zinc (Pearce et al., 2015). Pretreatment with zinc amino acid complex tends to reduce blood endotoxin levels and feed intake in response to compromised intestinal integrity in pigs under a heat condition (Pearce et al., 2015). Dietary selenium supplementation improves the immunocompetence of broilers induced by heat stress (Niu et al., 2009). Selenium-enriched probiotics treatment resulted in a lower diarrhea incidence than sodium selenite (Lv et al., 2015). The numbers of abdominal exudate cells, percentage of macrophages among the abdominal exudate cells and phagocytic macrophages were significantly increased by dietary selenium when birds were exposed to heat stress, and 0.2 mg/kg selenium-supplementation significantly improved their feed conversion (Niu et al., 2009). Minerals, including selenium, are one of the components of antioxidant enzymes, which may explain why supplemented with minerals can decrease the negative effect of heat stress.

3.5. Vitamins

Vitamins, as essential nutrients, play important roles in many processes. Vitamin E is a major chain-breaking antioxidant in biological systems. Stress is a major modifier of the action of vitamin E. Heat stress increases the susceptibility of birds to infectious disease, thus leading to an increase in their requirement for vitamin E (Khan et al., 2019). Supplementation with high levels of antioxidants (vitamin E and 0.24 mg selenium/kg) modulates skeletal muscle proinflammatory cytokines and NF- κ B transcription (Chauhan et al., 2014). Besides, mast cells produce factors such as corticotropin releasing factors that can in turn increase epithelial permeability to microbiota. During heat stress, endogenous vitamin C becomes insufficient to meet the birds' requirements. Supplementation with vitamin C could alleviate heat stress-induced problems (Abidin and Khatoon, 2019). Besides, vitamin A exerts a protective role in a dose-dependent manner. Compared with 3,000 IU/kg vitamin A supplementation, a high level of VA (9,000 IU/kg) has a positive effect on the feed intake and laying rate of heat stressed hens (Lin et al., 2002).

3.6. Others

There are many other types of nutrients that exert a beneficial effect on the alleviation of heat stress, such as cytokine and plant extractions. Heat shock proteins are a set of evolutionarily conserved proteins. HSP70 is usually expressed at low initial levels and upregulated in response to environmental and physiological stressors (Takayama et al., 2003). HSP70 enhances jejunum antioxidant enzyme activities and inhibits lipid peroxidation to alleviate intestinal mucosal oxidative injury (Gu et al., 2012). Pretreatment with HSP70 could inhibit heat stress-induced T84 monolayer barrier dysfunction (Yang et al., 2007). However, the protective capacity of HSP70 is limited, as it is not increased in response to a sustained high temperature (41 to 43 °C) (Yang et al., 2007). Similarly, pretreatment of mice with IL-6 before exposure to

a hot environment enhanced their ability to withstand heat exposure, reduced other cytokines involved in inflammation, and decreased the permeability of the intestinal barrier (Phillips et al., 2015). This suggested that IL-6 contributes to survival during acute life-threatening conditions such as heat stroke. These results suggested that hormones exert a protective role in heat conditions. Plant extractions are one of the green and safe ways to alleviate heat stress. Epigallocatechin-3-gallate, as a potential attenuator of heat stress, exhibited an anti-inflammatory effect in a gut microbiota dependent manner (Hu et al., 2019; Wu et al., 2021). Alfalfa polysaccharides, extracted from alfalfa, exerted a beneficial effect on the growth performance and antioxidant status in heat-stressed rabbits (Liu et al., 2010).

These dietary applications may be helpful for human beings and animals at high risk of heat stress. Indeed, the nutritional modulation of heat stress to support human health and animal production deserves more attention and further investigation.

4. Conclusion

Heat stress may induce human and livestock diseases, and it is necessary to evaluate these diseases and to determine how human and livestock adapt to a hot climate. The presently available information about the multidimensional response to heat stress within different parts of the gut is limited. Additional studies are necessary to investigate how they combine to modulate the severity and the risk of certain diseases. Moreover, an improved understanding of the molecular mechanisms underlying the close relationship between temperature–microbiota–brain interactions is needed.

Author contributions

Chaoyue Wen: writing, original draft preparation. **Siyu Wei and Xin Zong:** investigation. **Yizhen Wang:** supervision and validation. **Mingliang Jin:** reviewing and editing.

Conflicts of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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