Research Progress on Small Intestinal Injury Repair in Livestock Under Heat Stress: Postprint

Authors: Chen Xin, Li Yuanxiao, Wu Qiujue, Li Wang, Dou Mengying, Liang Fei, Zhu Jiali

Date: 2018-12-25T00:00:00+00:00

Abstract

Heat stress has become one of the common stressors in modern intensive farming systems. When livestock are subjected to heat stress, their intestinal morphology and intestinal mucosal barrier integrity are compromised, gut microbiota dysbiosis occurs, and the immune defense system is severely impaired, resulting in decreased feed intake, reduced feed conversion efficiency, diminished production performance, and increased incidence of various diseases, thereby inflicting substantial economic losses on the livestock industry. Therefore, this review summarizes the measures and mechanisms for repairing small intestinal damage caused by heat stress, aiming to provide effective strategies for mitigating heat stress-induced injury in practical production and thereby reducing losses to livestock production.

Full Text

Research Progress on Repair of Small Intestinal Injury Induced by Heat Stress in Livestock

CHEN Xin, LI Yuanxiao*, WU Qiujue, LI Wang, DOU Mengying, LIANG Fei, ZHU Jiali
College of Animal Science and Technology, Henan University of Science and Technology, Luoyang 471000, China

Abstract

Heat stress has become one of the most common stressors in modern intensive livestock production systems. When livestock are subjected to heat stress, their intestinal morphology and mucosal barrier integrity are compromised, intestinal flora becomes imbalanced, and the immune defense system is severely damaged. These effects lead to reduced feed intake, decreased feed conversion

efficiency, lower production performance, and increased incidence of various diseases, causing substantial economic losses to the livestock industry. This review summarizes the measures and mechanisms for repairing small intestinal injury caused by heat stress, aiming to provide effective strategies for mitigating heat stress-induced intestinal damage in practical production and thereby reducing associated losses in animal agriculture.

Keywords: heat stress; small intestinal injury; repair

1. Heat Stress and Its Damage to the Animal Intestine

Heat stress represents a non-specific response reaction when the body is stimulated by high external temperatures. For homeothermic animals, when ambient temperature exceeds the critical threshold, the organism can maintain constant body temperature by increasing heat dissipation and reducing heat production. However, as external temperature continues to rise, this dynamic equilibrium is disrupted, often resulting in severe heat stress.

When livestock are exposed to high-temperature environments, sympathetic nerve excitation increases, leading to elevated norepinephrine secretion and reduced secretion of thyroid hormone and motilin, which slows gastrointestinal motility and delays small intestinal emptying, thereby affecting digestion and absorption. Additionally, during activation of heat dissipation mechanisms, blood is redistributed from the body' s core to areas where evaporative cooling can occur. As blood flow to the skin increases, circulation to internal organs, including the digestive tract, decreases, resulting in intestinal ischemia and hypoxia. The microcirculation structure of intestinal mucosa is particularly sensitive to ischemia and hypoxia, and the regenerative capacity of gastrointestinal mucosal epithelial cells becomes impaired. Heat stress destroys intestinal mucosal morphology, causes epithelial cell shedding, exposes the lamina propria, shortens intestinal villi, increases intestinal permeability, and compromises intestinal barrier function. This intestinal damage not only affects nutrient digestion and absorption but also reduces feed intake and production performance, allows harmful substances to easily cross the intestinal barrier into the body, induces disease, and severely damages the immune defense system, thereby causing enormous losses to the livestock industry.

2. Repair and Mechanisms of Heat Stress-Induced Small Intestinal Injury in Livestock

The repair of small intestinal injury caused by heat stress has attracted increasing attention from scholars worldwide. In recent years, researchers have employed various methods to repair heat stress-induced intestinal damage in livestock. This review focuses on three main approaches: Chinese herbal medicines and their extracts, amino acids, and probiotics.

2.1 Repair Effects and Mechanisms of Chinese Herbal Medicines and Their Extracts on Heat Stress-Induced Small Intestinal Injury

Chinese herbal medicines contain various nutritional components and natural chemical compounds that can prevent and treat diseases, promote animal growth, enhance immune function, and improve disease resistance. These herbs can be used individually or combined in specific proportions to formulate herbal compounds. Certain Chinese herbs enhance immunity and inhibit harmful intestinal flora, making them useful for repairing heat stress-induced damage.

The intestinal mucosa serves as the first line of defense against pathogenic microorganisms. Wang et al. [**?**] found that heat stress damages duodenal and jejunal mucosa in rabbits, but dietary supplementation with a Chinese herbal compound maintained normal intestinal mucosal structure by providing heat-clearing and summerheat-relieving effects while preserving compensatory and antioxidant capacity. Xu et al. [**?**] investigated two herbal formulas in heat-stressed roosters: Formula I (equal proportions of gypsum, agastache, atractylodes, and phellodendron) and Formula II (atractylodes, phellodendron, gypsum, and agastache at a 1:1:0.5:1 ratio). Both formulas increased intestinal goblet cell numbers. Goblet cells secrete mucin, which forms a "mucus barrier" with water to provide mechanical protection, with Formula I showing superior repair effects. Polysaccharides in Chinese herbs have immune-promoting effects, and agastache contains polysaccharide components. Shen et al. [**?**] supplemented heat-stressed laying hens with a formula containing seven herbs including agastache, mint, anemarrhena, and rhodiola, observing increased numbers and concentrations of intestinal intraepithelial lymphocytes, which reflect the integrity of local mucosal immune defense function. Interleukin-2 (IL-2) is an important lymphokine and a key indicator for evaluating cellular immunity. Duan et al. [**?**] found that IL-2 levels in duodenal, jejunal, and ileal mucosa decreased under heat stress but recovered after administration of an anti-stress herbal preparation. Shi et al. [**?**] demonstrated that both herbal additives alone and combined with vitamin C promoted lymphocyte and goblet cell generation, with the combination showing better effects in alleviating heat stress in laying hens.

Resveratrol has antioxidant and anti-inflammatory properties. Liu [**?**] showed that compared with normal temperature controls, heat stress reduced jejunal villus height, villus height-to-crypt depth ratio, goblet cell numbers, and lymphocyte counts while increasing crypt depth. Supplementation with 400 mg/kg resveratrol to heat-stressed silky fowls reversed these effects. Further investigation of heat stress-related genes and proteins revealed that heat stress increased expression of HSP70, HSP90, and NF- B while decreasing EGF expression in jejunal mucosa, whereas resveratrol treatment reduced HSP70, HSP90, and NF- B expression and increased EGF expression. Magnolol, an extract from Magnolia officinalis, has antibacterial and anti-inflammatory effects. Mei [**?**] found that magnolol alleviated heat stress-induced G1 phase cell cycle arrest in mouse small intestinal epithelial cells, with optimal effects at 20 mol/L. Ferulic acid, an active component in Chinese herbs such as Asafoetida, Ligusticum wallichii, and

Angelica sinensis, was studied by He [?], who found that it inhibited activation of MAPK and NF- B signaling pathways, reduced inflammatory factor release, alleviated heat stress-induced damage to rat small intestinal mucosal barrier, and effectively relieved heat stress-induced IEC-6 cell barrier function injury.

Chinese herbal medicines are widely used to alleviate heat stress in dairy cows. Fan et al. [?] supplemented heat-stressed dairy cows with Bupleurum extract, resulting in increased feed intake, milk yield, and milk protein content, along with reduced somatic cell counts, indicating effective heat stress relief. Zhan et al. [?] added different doses of alfalfa flavonoids to heat-stressed dairy cow mammary epithelial cells in vitro, finding that 25 g/mL produced the strongest cell viability, while doses of 50, 75, and 100 g/mL increased glutathione peroxidase (GSH-Px) activity and reduced lactate dehydrogenase (LDH) activity and malondialdehyde (MDA) content. However, whether these effects occur through intestinal damage repair requires further investigation. Overall, Chinese herbal medicines and their extracts can repair intestinal tissue morphology, maintain intestinal barrier integrity, and restore immune defense systems under heat stress.

2.2 Repair Effects and Mechanisms of Amino Acids on Heat Stress-Induced Small Intestinal Injury

Since the 1970s, Windmueller et al. [?] have confirmed that mouse small intestine can metabolize glutamine (Gln), glutamate (Glu), and aspartate (Asp). Numerous studies have shown that in pigs, sheep, and dairy cows, Gln can be metabolized to produce arginine (Arg), citrulline (Cit), alanine (Ala), aspartate, ornithine (Orn), and other amino acids. Increasingly, amino acids are being applied to repair heat stress-induced small intestinal injury.

Under high temperature, intestinal repair slows and active nutrient absorption function declines. Endogenous Gln synthesis cannot meet the body' s needs, and in severe cases, Gln may become depleted. Gln deficiency affects the function of intestinal mucosal lamina propria and proliferation of mesenteric lymphocytes. As the primary energy source for the intestine, Gln provides energy for intestinal epithelial cells and lymphocytes, thereby promoting intestinal repair. Dai et al. [?] supplemented 35-day-old heat-stressed broilers with dietary Gln, finding that it restored heat stress-induced damage to relative weight, villus height, gland length, and muscular layer thickness of duodenum and jejunum, as well as jejunal villus width and ileal villus height and gland length to normal levels. Kang et al. [?] applied different Gln levels to heat-stressed broilers of various ages, observing increased intraepithelial lymphocyte numbers in duodenal, jejunal, and ileal mucosa and improved intestinal immune performance. These results demonstrate that exogenous Gln supplementation provides energy for intestinal mucosal epithelial cells and activated lymphocytes, compensates for heat stress-induced Gln deficiency, and promotes intestinal repair.

-aminobutyric acid (GABA) is an inhibitory neurotransmitter that calms live-

stock, reduces anxiety, and confers heat stress resistance. As a nutritional regulator, GABA can be indirectly converted to Gln, the primary energy source for intestinal mucosal epithelial cells and lymphocytes. Liang et al. [**?**] investigated GABA' s repair effects using different concentrations on heat stress-induced intestinal injury in chicks. By measuring interleukin-7 (IL-7) and secretory immunoglobulin A (SIgA) levels in small intestinal mucosa, they found that heat stress reduced IL-7 and SIgA content, while supplementation with 50 or 100 mg/kg GABA increased these levels, indicating that GABA enhanced intestinal function and effectively repaired heat stress-induced intestinal damage in chicks. Li et al. [**?**] applied GABA to alleviate heat stress in Holstein dairy cows, finding increased superoxide dismutase (SOD) and GSH-Px activity and reduced MDA content in blood. Han et al. [**?**] fed heat-stressed dairy cows with rumen-protected methionine, resulting in 3.69% higher milk yield, 4.95% higher milk fat percentage, 2.66% higher milk protein content, 33.73% lower somatic cell count, 10.37% lower blood LDH activity, 14.91% lower MDA content, 13.64% higher SOD activity, 6.87% higher GSH-Px activity, and 36.39% lower peripheral blood lymphocyte apoptosis rate. Rumen-protected methionine improved antioxidant capacity, directly increased intestinal metabolizable methionine supply, and alleviated adverse effects of heat stress in dairy cows.

Nitric oxide (NO) can combine with free radicals, block hydroxyl radical formation, and terminate radical chain reactions on lipid membranes, conferring antioxidant capacity. Exogenous Arg supplementation promotes NO production. Zhang [**?**] found that acute heat stress reduced duodenal and jejunal villus height and decreased lymphocyte numbers, intraepithelial lymphocyte (IEL) counts, SIgA-secreting cell density, T lymphocyte positive rate, total antioxidant capacity (T-AOC), and NO content. Dietary Arg supplementation to acutely heat-stressed roosters increased intestinal villus height, lymphocyte numbers, SIgA-secreting cells, IEL counts, T lymphocyte positive rate, T-AOC, and NO content. These findings demonstrate that Arg promotes mucosal epithelial growth and differentiation, improves mucosal structure, maintains intestinal barrier integrity, stimulates growth hormone release, and reduces endotoxin levels, thereby protecting both mechanical and immune barriers of intestinal mucosa from heat stress damage.

2.3 Repair Effects and Mechanisms of Probiotics on Heat Stress-Induced Small Intestinal Injury

Probiotics are microorganisms or preparations that exert beneficial effects on animals by improving intestinal flora balance [**?**]. In 1947, Hallsen first applied Lactobacillus to feed, finding that it increased piglet body weight and improved health status [**?**]. Recently, increasing research has focused on probiotic effects on intestinal heat stress.

Probiotic repair primarily affects the microbial barrier and intestinal flora under heat stress. Lactic acid bacteria are major probiotics in chicken intestine. Hu et al. [**?**] fed laying hens diets containing four probiotic Bacillus species

(Bacillus megaterium, Bacillus coagulans, Bacillus licheniformis, and Bacillus subtilis) before acute heat stress treatment. Compared with the control group without probiotics, total aerobic bacteria decreased, total lactic acid bacteria increased, and their ratio decreased in all treatment groups. Reduced aerobic bacteria benefit animal health, demonstrating that these four Bacillus species can maintain normal intestinal microecology under heat stress. Selenium-enriched probiotics have dual effects of selenium and probiotics, protecting dominant flora and enhancing immunity. Lv [**?**] supplemented heat-stressed piglets with selenium-enriched probiotics, observing increased Lactobacillus counts and reduced Enterobacter counts, which can cause flora imbalance, confirming that selenium-enriched probiotics improve microbial community structure.

Bacillus licheniformis is another probiotic that adjusts intestinal flora imbalance and restores intestinal function. Deng [**?**] found that dietary supplementation with 1,000 mg/kg Bacillus licheniformis not only repaired microbial flora in heat-stressed laying hens but also increased intestinal villus height and villus height-to-crypt depth ratio, increased lymphocyte numbers and SIgA-positive area, reduced crypt depth, and decreased mast cell numbers. Multiple probiotics can also repair heat stress-induced intestinal injury. Jiang et al. [**?**] fed weaned piglets under heat stress with diets containing 1% and 3% compound probiotics, finding significantly increased intestinal Lactobacillus counts and decreased Escherichia coli counts. The 3% compound probiotic diet significantly reduced HSP70 and HSP27 gene expression. Zhang [**?**] found that a compound probiotic consisting of 100 g/t Enterococcus faecium + 400 g/t Bacillus subtilis not only repaired heat stress-induced intestinal flora imbalance in piglets but also increased intestinal villus height and villus height-to-crypt depth ratio, increased tight junction protein content in intestinal tissue, and upregulated EGF gene expression, thereby maintaining intestinal mechanical barrier integrity.

Fiber oligosaccharides regulate gastrointestinal flora and improve immunity. Song [**?**] found that combined probiotic and fiber oligosaccharide treatment not only maintained intestinal flora balance in heat-stressed broilers but also preserved intestinal morphology and increased Occludin protein expression. Yeast products stabilize rumen pH. Wang [**?**] found that dietary yeast culture supplementation in heat-stressed dairy cows reduced respiratory rate, rectal temperature, serum alkaline phosphatase activity, and urea nitrogen content while increasing serum total protein content. Wang [**?**] supplemented heat-stressed dairy cows with selenium yeast and yeast culture, finding that combined use increased milk yield by 8.25% and milk protein percentage by 9.6% compared with basal diet, significantly increased blood GSH-Px activity, and significantly reduced MDA and endotoxin content. The combination improved antioxidant capacity and significantly reduced endotoxin absorption, indicating that yeast products can repair or mitigate heat stress-induced intestinal damage in dairy cows. In summary, probiotics can maintain normal intestinal flora and mucosal structural integrity, restore the microbial barrier, and enhance immunity in livestock under heat stress.

3. Summary

Under heat stress, intestinal injury is the core issue causing decreased production performance in livestock. Repairing intestinal damage can alleviate negative effects of heat stress. Therefore, increasing research has focused on repairing heat stress-induced small intestinal injury. Dietary supplementation with Chinese herbal medicines, amino acids, and probiotics has achieved promising results, providing effective evidence for practical production applications.

References

[1] 蔡丽媛. 集约化羊舍的环境控制及热应激对山羊瘤胃发酵的影响 [D]. 博士学位论文. 武汉: 华中农业大学,2015.

NARDON A,RONCHI B,LACETERA N,et al.Effects of climate changes on animal production and sustainability of livestock systems[J].Livestock Science,2010,130(1/2/3):57-69.

LEI L,HEPENG L,XIANLEI L,et al.Effects of acute heat stress on gene expression of brain-gut neuropeptides in broiler chickens (Gallus gallus domesticus)[J].Journal of Animal Science,2013,91(11):5194-5201. [4] YU J,YIN P,YIN J D,et al.Involvement of ERK1/2 signalling and growth-related molecules' expression in response to heat stress-induced damage in rat jejunum and IEC-6 cells[J].International Journal of Hyperthermia,2010,26(6):538-555. [5] CRONJÉ P B.Heat stress in livestock-the role of the gut in its aetiology and a potential role betaine alleviation[J].Recent Advances Animal Nutrition Australia,2005,15:107-122.

SAMAIN A.Digestive hemorrhages during stress[J].Acta Chirurgica Belgica,1966,65(5):574-576.

RADWAN M A,EL-GENDY K S,GAD A F.Oxidative stress biomarkers in the digestive gland of Theba pisana exposed to heavy metals[J].Archives of Environmental Contamination and Toxicology,2010,58(3):828-835. [8] 高俊杰, 郝瑞蓉, 韩俊文. 断奶应激对仔猪肠黏膜形态的影响 [J]. 四川畜牧兽医,2003,30(3):26-28. [9] 胡晓飞, 职爱民, 魏凤仙, 等. 应激影响家禽肠道结构和功能的研究进展 [J]. 中国家禽,2009,31(14):36-39. [10] 高金生, 杨书良. 肠黏膜屏障损伤的原因与机制研究进展 [J]. 世界华人消化杂志,2009,17(15):1540-1544. [11] 徐如海, 胡锦平, 翁经强, 等. 肠道——畜禽热应激研究中被忽视的核心环节 [J]. 中国畜牧杂志,2008,44(19):52-54. [12] 余进. 猪和大鼠小肠黏膜热应激损伤修复机制的研究 [D]. 硕士学位论文. 北京: 北京农学院,2010. [13] 吴结革, 茆达干. 热应激对动物生殖机能的影响及其作用机理 [J]. 中国畜牧兽医文摘,2007,27(4):28-29. [14] OISHI Y,TANIGUCHI K,MATSUMOTO H,et al.Differential responses of HSPs to heat stress slow and regions gastrocnemius muscle[J].Muscle & Nerve,2003,28(5):587-594. [15] 胡艳欣, 佘锐萍, 张洪玉, 等. 热应激后猪血清中 IL-2、IFN- 及 TNF- 水平的动态变化 [J]. 畜牧兽医学报,2006,37(5):496-499. [16] 王自力, 张翥, 唐琪, 等. 中药复方对热应激肉兔肠道组织结构及肝脏抗氧化机能的影响 [J]. 中国兽医杂志,2014,50(6):48-51,54. [17] 徐光科, 陈韩英, 朱晓宇, 等. 中药复方对高温中鸡肠黏膜杯状细胞数量的影响 [J]. 中兽医医药杂志,2007,26(1):5-7. [18] 沈萍, 史秋梅, 高光平, 等. 中草药抗热应激蛋鸡小肠上皮内淋巴细胞

的组织学观察 [J]. 河北科技师范学院学报,2012,26(4):54-57. [19] 段美玲, 方洛云, 毛帅, 等. 中药抗应激冲剂对热应激小鼠小肠黏膜中 IL-2 水平的影响 [J]. 中国兽医杂志,2009,45(4):52-54. SHI Q M,GAO G S,XING C,et al.Effects of traditional Chinese medicine on numbers of lymphocytes and goblet cells in villus epithelia of layers under heat stress[J].Agricultural Science & Technology,2015,16(2):311-316,335. [21] 刘丽莉. 白藜芦醇对乌骨鸡热应激损伤的修复机制研究 [D]. 博士学位论文. 长沙: 湖南农业大学,2014. [22] MEI C,HE S S,YIN P,et al.Magnolol pretreatment attenuates heat stress-induced IEC-6 cell injury[J].Journal of Zhejiang University-Science B,2016,17(6):413-424. [23] 何莎莎. 阿魏酸对热应激大鼠小肠黏膜屏障损伤的保护作用及机制 [D]. 博士学位论文. 北京: 中国农业大学,2016. [24] 范彩云, 苏娣, 侍宝路, 等. 柴胡提取物对热应激奶牛生产性能和血液代谢的影响 [J]. 草业科学,2017,34(12):2538-2545. [25] 占今舜, 魏明吉, 苏效双, 等. 苜蓿黄酮对热应激下体外培养奶牛乳腺上皮细胞凋亡的影响 [J]. 草业学报,2016,25(4):159-165. [26] WINDMUELLER H G.Glutamine utilization by the small intestine[J].Advances in Enzymology & Related Areas of Molecular Biology,1982,53:201-237. [27] DE-SOUZA D A,GREENE L J.Intestinal permeability and systemic infections in critically ill patients:effect of glutamine[J].Critical Care Medicine,2005,33(5):1125-1135.

WEMERMAN J.Clinical use of glutamine supplementation[J].The Journal of Nutrition,2008,138(10):2040S-2044S. [29] 戴四发, 王立克, 王立新, 等. 谷氨酰胺对热应激条件下肉鸡生产性能、肠道消化酶活和形态结构的保护作用 [J]. 中国粮油学报,2009,24(4):103-107. [30] 康磊, 李文立, 姜建阳, 等. 谷氨酰胺添加水平对热应激肉鸡小肠粘膜上皮内淋巴细胞数量的影响 [J]. 青岛农业大学学报 (自然科学版),2012,29(1):36-40. [31] 梁臣, 汪威, 周永蔚, 等.GABA 对热应激雏鸡小肠黏膜中 IL-IL-7 和 sIgA 含量的影响 [J]. 中国家禽,2016,38(13):22-25. [32] 李锦春, 徐同铜, 钟刚, 等. -氨基丁酸对热应激奶牛泌乳性能和血液抗氧化酶、激素及离子的影响 [J]. 畜牧与兽医,2016,48(5):12-18. [33] 韩兆玉, 周国波, 金志红, 等. 过瘤胃蛋氨酸对热应激下奶牛生产性能、淋巴细胞凋亡以及相关基因的影响 [J]. 动物营养学报,2009,21(5):665-672. [34] 张灿菲. 精氨酸对急性热应激鸡肠道黏膜免疫的影响 [D]. 硕士学位论文. 武汉: 华中农业大学,2008. [35] 刘艳, 明双喜, 王沂蒙, 等. 关注益生菌 [J]. 中国家禽,2007,29(3):43-48.

HANSEN I G,MØLLGAARD H.Investigations of the effect of lactic acid on the metabolism of calcium and phosphorus[J].Acta Physiologica Scandinavica,1947,14(1/2):158-170. [37] 胡长庆, 赵京杨, 杨季芳, 等. 益生芽孢杆菌对热应激鸡盲肠菌群变化的影响 [J]. 中国家禽,2008,30(10):25-27. [38] 吕晨辉. 富硒益生菌对高温条件下仔猪生产性能、抗氧化能力和肠道菌群的影响 [D]. 硕士学位论文. 南京: 南京农业大学,2013. [39] 邓文. 地衣芽孢杆菌缓解蛋鸡热应激的效果及机理研究 [D]. 博士学位论文. 北京: 中国农业科学院,2011. [40] 蒋加进, 甘芳, 胡志华, 等. 复合益生菌对高热环境中仔猪生长性能、肠道菌群和热休克蛋白表达的影响 [J]. 江苏农业学报,2013,29(5):1070-1074. [41] 张盼望. 复合益生菌缓解蛋鸡热应激效果及机理研究 [D]. 硕士学位论文. 武汉: 华中农业大学,2015. [42] 宋娟. 益生菌和纤维寡糖对热应激肉鸡肠道功能和氮排放的影响 [D]. 硕士学位论文. 杭州: 浙江大学,2014. [43] WILLIAMS P E,TAI C A G,INNES G M,et al.Effects of the inclusion of yeast culture (Saccharomyces cerevisiae plus growth medium) in the diet of dairy cows on milk yield and forage degradation and fermentation patterns in the rumen of steers[J].Journal of Animal Science,1991,69(7):3016-3026. [44] 王淑梅. 酵母培养物对围产期奶牛热应激及山羊瘤胃消化代谢的影响 [D]. 硕士学位论文. 郑州: 河南农业大学,2007. [45] 王立志. 热应激对奶牛、奶山羊体内内毒素含量的影响及缓解热应激的营养

技术研究 [D]. 博士学位论文. 雅安: 四川农业大学,2010.

Note: Figure translations are in progress. See original paper for figures.