



热应激下细菌内毒素对畜禽的损伤及损伤机制研究进展

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摘要: 规模化与集约化养殖的快速发展导致畜禽热应激发生频率大幅提高, 对畜禽的各项生产性能与机体健康等造成一系列严重危害。研究发现, 热应激对畜禽机体的损伤程度与胃肠道中的细菌内毒素含量高度相关。热应激条件下, 外周血量增加使胃肠道供血不足导致胃肠道屏障功能受损, 进而使得大量细菌内毒素经胃肠道上皮进入血液系统, 最终造成机体各个脏器损伤。本文综述了热应激条件下畜禽体内内毒素产生途径及其对畜禽机体损伤和相关机制的研究进展, 以期为缓解热应激下内毒素对畜禽的危害提供创新思路。

关键词: 内毒素; 温湿度指数; TLR4; NF-κB

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Research Progress in the Damage of Bacterial Endotoxins to Livestock and Poultry under Heat Stress and Its Potential Mechanisms

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Abstract: The rapid development of large-scale and intensive livestock and poultry farming has led to a significant increase in the frequency of heat stress, which results in a series of harms to the production performance and physical health of livestock and poultry. Studies have found that the body damages of livestock and poultry caused by heat stress are closely related to endotoxins. Under heat stress conditions, the increase in peripheral blood volume leads to insufficient blood supply for the gastrointestinal tract, resulting in damages to its barrier function. Consequently, an increasing translocation of bacterial endotoxins into the blood system would lead to damages to various organs of the body. This article reviews the generation of endotoxin in livestock and poultry under heat stress conditions, its damage to the bodies of livestock and poultry under heat stress conditions, and the research progresses on the relevant body damages and mechanisms, with the aim of providing an innovative reference for the prevention and control of endotoxins hazards in livestock and poultry exposed to heat stress.

Keywords: endotoxin; temperature-humidity index; TLR4; NF-κB

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在温度、湿度过高环境中,动物体内产生的各种能够帮助机体环境维持在一个相对稳定状态的非特异性应答反应,被普遍认定为热应激^[1]。不同畜禽对热应激的敏感性存在差异,通常使用温湿度指数(temperature-humidity index, THI)来评估。对于高产奶牛来说,当 THI>68 时,如奶牛呼吸频率显著增加、体温升高、繁殖及生产性能显著下降,即被认为进入热应激状态^[2-4]。而对于肉牛来说,当 THI≥72 被认为进入热应激状态^[5]。研究证明,热应激对动物的生长性能、生理指标、内分泌系统、免疫、抗氧化功能及胃肠道菌群均产生不良影响^[6-10]。研究发现,热应激对畜禽机体的损伤与内毒素密切相关^[11-13]。热应激下,一方面革兰阴性菌(Gram-negative bacteria, GNB)的生长和增殖加快,导致胃肠道菌群失衡,而 GNB 分裂或死亡时会释放出大量脂多糖(lipopolysaccharide, LPS),即内毒素(endotoxin, ET)^[14-15];另一方面,热应激引发肠道缺血,诱导大量活性氧(reactive oxygen species, ROS)生成,导致生物膜脂质过氧化及屏障被破坏。ET 协同激活烟酰胺腺嘌呤二核苷酸磷酸氧化酶(NADPHO),导致 ROS 爆发,加剧肠道细胞膜结构损伤,使 ET 进入血液循环。ET 入血后,激活免疫

细胞释放炎性介质,形成“氧化损伤-屏障渗漏-炎症扩散”正反馈循环,协同放大热应激损伤^[12-13,16]。本文综述了热应激条件下畜禽体内 ET 生成途径,及其对畜禽机体损伤和相关机制研究进展,以期对热应激下畜禽体内 ET 危害的防控提供参考。

1 热应激下内毒素的产生

LPS 位于 GNB 的细胞壁中,由特异性 O 抗原多糖侧链、核心多糖、类脂 A 三部分构成(图 1)。其中,类脂 A 是激活宿主多种免疫和炎症细胞,参与急性应激反应、调节炎症和免疫应答的核心成分;当 GNB 分裂或死亡时释放的脂多糖在游离状态下被称为 ET^[14,17-19]。动物胃肠道作为机体最大的细菌库,其内定植的多种细菌可产生 ET,不同应激因素均可引起胃肠道菌群比例和结构发生改变,造成肠道菌群维生素合成减少、氧化应激、营养缺陷及毒素分泌增多,进而影响其抗炎及免疫调节作用^[20-22]。正常情况下,动物机体的胃肠道和血液中也存在低浓度的 ET,但不会对机体造成损伤,而热应激引发的胃肠道菌群结构重塑显著提高了 GNB 的丰度,且随着热应激时间的延长,ET 浓度也随之提高^[23-26]。

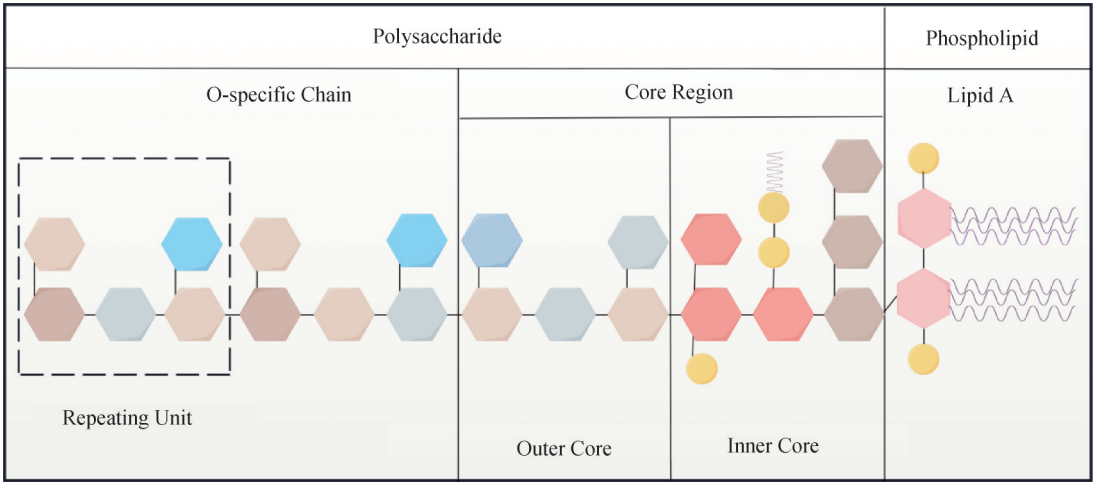


图1 革兰阴性菌 LPS 的一般化学结构式(本图由 Figdraw 绘制)

Fig. 1 General chemical structure of gram negative bacterial LPS (by Figdraw)

2 热应激下细菌内毒素对畜禽的损伤及机制

2.1 对畜禽消化道的损伤及机制

热应激下,ET 对肠道的损伤主要是肠道屏障功能损伤,潜在机制包括炎症反应激活、氧化应激

诱导及细胞凋亡,这些损伤机制相互关联,共同影响肠道的正常生理功能。热应激条件下,动物胃肠道微生物菌群结构和多样性发生显著改变,进而释放出大量 ET^[15,27]。ET 先与 LPS 结合蛋白(lipopolysaccharide binding protein, LBP)结合形成复合物,然后该复合物与特异受体分簇化 14

(cluster of differentiation 14, CD14)结合。CD14介导单核/巨噬细胞、内皮细胞等识别ET,并通过Toll样受体介导细胞内信号机制。热应激下机体热休克蛋白(heat shock proteins, HSPs)表达失衡,并激活肌球蛋白轻链激酶(Myosin light chain kinase, MLCK),使紧密连接蛋白(Claudin)和闭合蛋白(Occludin)表达下降,导致肠道屏障损伤^[28-29]。同时,ET可通过TLR4(Toll-like receptor 4)或髓样分化因子-2等识别受体直接作用于肠上皮细胞,一方面通过NF- κ B信号传导,另一方面通过丝裂原活化蛋白激酶(Mitogen-activated protein kinases, MAPK)信号级联反应,这些通路的协同激活可显著上调多种炎症介质的基因表达,包括IL-1 β 、IL-6、IL-8、IL-12、IL-13、TNF- α 等细胞因子,以及环氧合酶-2(Cyclooxygenase-2, COX-2)、巨噬细胞趋化因子以及细胞黏附分子,这种级联反应最终引发炎症反应并导致细胞损伤^[30-32]。炎症反应使肠道黏膜充血、水肿,肠道上皮细胞间的紧密连接进一步受损,Claudin和Occludin表达持续下降,导致ET更容易进入肠道组织形成恶性循环^[33](图2)。此外,热应激诱导产生的ROS可作用于NOD样受体蛋白3(NOD-like receptor protein 3, NLRP3),促进Caspase-1激活,进一步推动炎症因子的成熟与释放^[34]。同时,热应激会抑制肠道细胞中NRF2通路,导致SOD表达下降,MDA表达上调。当ET激活巨噬细胞等免疫细胞后,会触发细胞内氧化应激相关信号通路,促使大量ROS生成。ROS的积累会引发生物膜中多不饱和脂肪酸发生过氧化反应,最终破坏细胞膜结构,使其功能完整性受损(图2)。

热应激下,ET对肠道细胞凋亡也起着重要作用。热应激与ET协同诱导产生的氧化应激,会损伤肠道细胞内的线粒体等细胞器,干扰细胞能量代谢过程,导致细胞功能紊乱,最终引发肠道细胞凋亡。与此同时,ET诱导的炎症反应与氧化应激协同作用,激活Caspase家族蛋白酶等凋亡相关信号通路,导致肠道上皮层变薄、绒毛高度降低和隐窝深度改变,损伤肠道黏膜的完整性和修复能力^[34-36]。这些损伤使更多的ET进入血液循环,研究发现,热应激条件下肉鸡^[37]、猪^[38]、奶山羊^[39]和奶牛^[39]血清中的ET浓度显著升高,进而对体内各脏器造成一系列损伤。

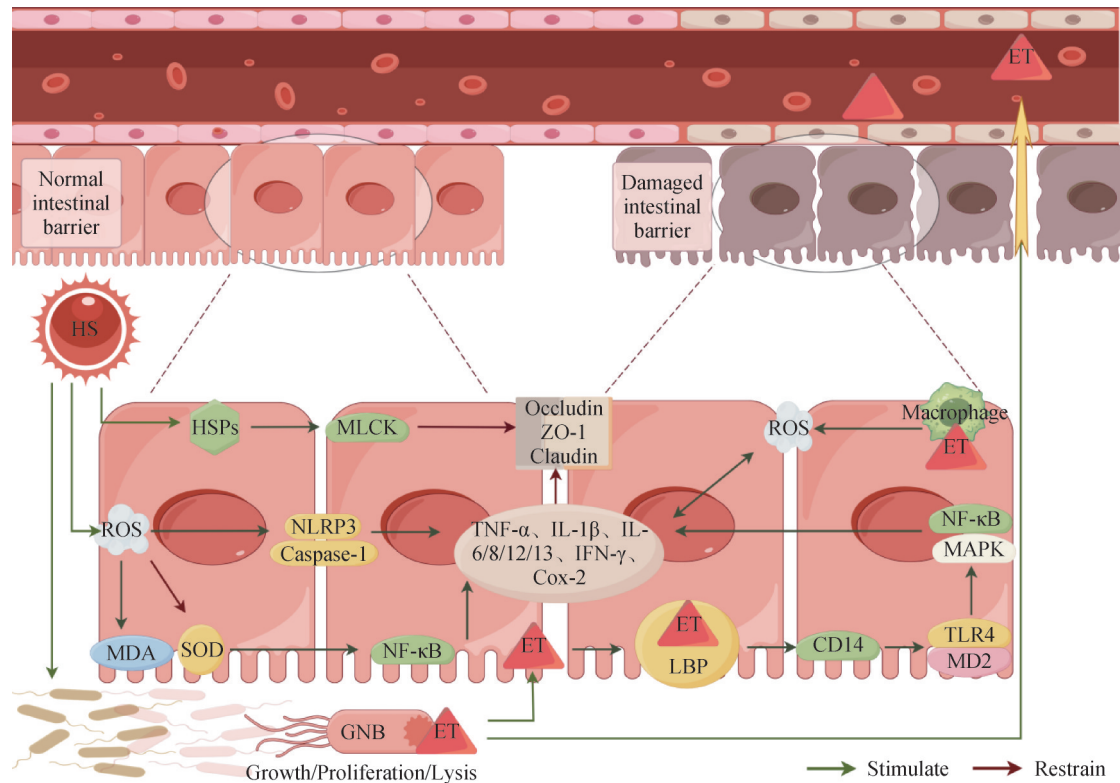
2.2 对畜禽心血管系统的损伤及机制

热应激下,ET可通过激活炎症信号通路等机

制引发血管舒缩功能紊乱^[40-42]。热应激条件下,为了增加散热,机体会通过神经调节使体表血管平滑肌舒张,从而使血管内径增大,更多的血液流向体表;同时,交感神经兴奋释放去甲肾上腺素等神经递质,作用于脏器血管平滑肌上的相应受体,使血管收缩,减少脏器的血量。长期处于热应激状态,血管对神经和体液调节的反应性降低,从而导致血管舒缩功能失调(图3)。ET进入血液循环后,一方面通过刺激单核巨噬细胞激活NF- κ B和MAPK转录因子,促进炎症因子(TNF- α 、IL-1 β 、IL-6、COX-1/2)、MCP-1、E-选择素(E-selection)和血管细胞黏附分子-1的表达,最终引发血管炎症以及血管内皮细胞(vascular endothelial cell, VEC)功能紊乱(图3)^[43];另一方面,通过与CD14介导单核细胞和巨噬细胞相互作用,促使磷脂酶A2(Phospholipase A2, PLA2)被激活,进而从花生四烯酸(Arachidonic acid, AA)产生前列腺素(Prostaglandin, PG)和白三烯(Leukotriene, LT)等血管活性物质释放,引起毛细血管通透性增加和血管平滑肌张力失调^[44-45]。研究发现,ET进入血液后有弥漫性血管内凝血和组织学变化^[40,46]。ET可导致实质脏器的血管内皮细胞发生空泡变性和激活凝血系统,促使凝血因子释放并引发血小板聚集,全身的小血管及毛细血管均可见瘀血、凝血或出现弥漫性血管内凝血的现象^[47]。在热应激下,血液黏稠度有所增加,此时凝血系统被激活,凝血因子释放和血小板聚集现象加剧,极易形成微血栓从而阻塞血管^[48]。ET可引起内毒素血症,主要症状为发热、白细胞数目先降后升、心力衰竭以及免疫功能减退,严重时出现神经症状以及休克等情况^[40,49]。热应激会抑制畜禽的免疫系统,致使机体的免疫功能下降,ET通过激活免疫细胞释放大量炎症因子,引发全身炎症反应综合征(Systemic inflammatory response syndrome, SIRS)(图3)。

2.3 对畜禽肝脏的损伤及机制

热应激下,ET对肝脏造成的损伤及损伤的机制主要包括炎症反应激活、氧化应激诱导、代谢紊乱等。病理学检查显示,肝细胞常出现肿胀、变性、坏死等现象,同时伴有肝窦扩张、淤血明显以及炎性细胞浸润等特征^[50-51]。热应激下,肝细胞内质网中未折叠/错误折叠蛋白的大量堆积,进而触发未折叠蛋白反应(unfolded protein response, UPR),通过激活蛋白激酶R样内质网激酶(Protein kinase



HS. 热应激; ET. 内毒素; GNB. 革兰阴性菌; ROS. 活性氧; MDA. 丙二醛; SOD. 超氧化物歧化酶; HSPs. 热休克蛋白; NLRP3. NOD样受体蛋白3; *Caspase-1*. 半胱天冬酶-1; MLCK. 肌球蛋白轻链激酶; $\text{TNF-}\alpha$. 肿瘤坏死因子- α ; $\text{IFN-}\gamma$. 干扰素- γ ; $\text{IL-1}\beta/6/8/12/13$. 白细胞介素- $1\beta/6/8/12/13$; COX-2. 环氧合酶-2; MD-2. 髓样分化蛋白-2; MAPK. 丝裂原活化蛋白激酶; TLR4. Toll受体4; $\text{NF-}\kappa\text{B}$. 核因子- κB ; LPS-LBP-CD14. LPS-LBP-CD14复合物; Claudin. 紧密连接蛋白; Occludin. 闭合蛋白; ZO-1. 紧密连接蛋白1; Stimulate. 促进; Restrained. 抑制

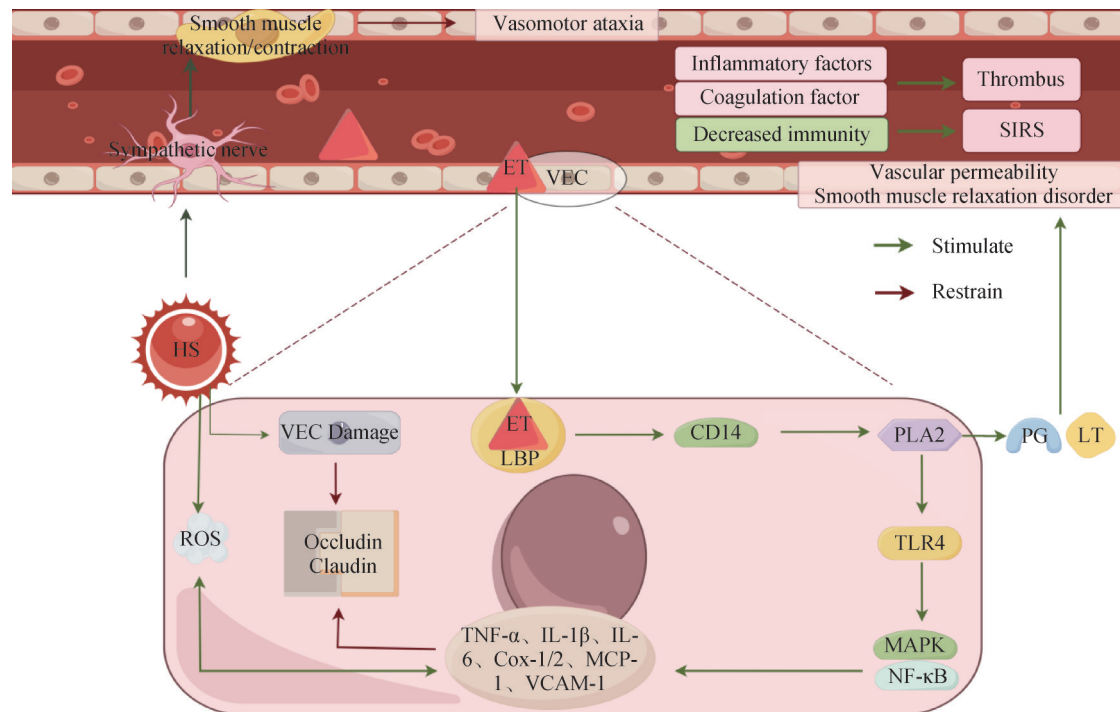
HS. Heat stress; ET. Endotoxin; GNB. Gram negative bacteria; ROS. Reactive oxygen species; MDA. Malondialdehyde; SOD. Superoxide dismutase; HSPs. Heat shock proteins; NLRP3. NOD-like receptor protein 3; *Caspase-1*. Cysteine-aspartic acid protease-1; MLCK. Myosin light chain kinase; $\text{TNF-}\alpha$. Tumor necrosis factor- α ; $\text{IFN-}\gamma$. Interferon gamma; $\text{IL-1}\beta/6/8/12/13$. Interleukin- $1\beta/6/8/12/13$; COX-2. Cyclooxygenase-2; MD-2. Myeloid differentiation protein-2; MAPK. Mitogen-activated protein kinase; TLR4. Toll-like receptor 4; $\text{NF-}\kappa\text{B}$. Nuclear factor kappa-B; LPS-LBP-CD14. LPS-LBP-CD14 complex; ZO-1. Zonula occludens-1

图2 热应激条件下内毒素对畜禽肠道的损伤及机制(本图由Figdraw绘制)

Fig. 2 The damage and mechanism of endotoxins on the intestinal tract of livestock and poultry under heat stress conditions (by Figdraw)

r-like endoplasmic reticulum kinase, PERK) 和肌醇需求酶1(Inositol- requiring enzyme 1, IRE1)通路, 引发内质网应激(Endoplasmic reticulum stress, ERS), 进一步促进促凋亡蛋白Bax的表达, 同时抑制抗凋亡蛋白Bcl-2的活性, 最终诱发线粒体凋亡。同时, ET能与免疫细胞和肝细胞等表面TLR4结合, 激活 $\text{NF-}\kappa\text{B}$ 与MAPK信号通路刺激炎症因子生成, 诱导炎症反应产生肝损伤^[52-54]。有研究表明, ET作用于肝脏后, 肝窦内皮细胞等通过上调TLR4 mRNA做出反应, 激活TLR4下游信号传导并通过

$\text{NF-}\kappa\text{B}$ 通路产生促炎细胞因子^[53](图4)。长期的热应激和ET作用还可能导致肝脏氧化应激及肝纤维化, 严重影响肝脏的正常功能^[55]。热应激可引发肝脏ROS大量生成, 而机体NRF2通路被抑制, SOD等抗氧化酶表达下降, 导致抗氧化失衡。ROS直接损伤线粒体膜, 引发膜损伤并释放细胞色素C(Cytochrome C, Cyt c), 激活Caspase3/9级联反应诱导肝细胞凋亡。ET作用于肝脏使血清中肝酶指标如谷丙转氨酶、谷草转氨酶、碱性磷酸酶等浓度显著升高, 表明肝细胞的通透性增加和肝细胞的破



HS. 热应激;ET. 内毒素;PLA2. 磷脂酶 A2;PG. 前列腺素;LT. 白三烯;ROS. 活性氧;VEC. 血管内皮细胞;VCAM-1. 血管细胞黏附分子-1;MCP-1. 黏附分子如单核细胞趋化蛋白-1;TNF- α . 肿瘤坏死因子- α ;IL-1 β /6. 白细胞介素-1 β /6;COX-1/2. 环氧合酶-1/2;MAPK. 丝裂原活化蛋白激酶;TLR-4. Toll受体4;NF- κ B. 核因子 κ B;LPS-LBP-CD14. LPS-LBP-CD14复合物;Claudin. 紧密连接蛋白;Occludin. 闭合蛋白;Stimulate. 促进;Restraining. 抑制

HS. Heat stress;ET. Endotoxin;PLA2. A2 Phospholipase A2;PG. Prostaglandin;LT. Leukotriene;ROS. Reactive oxygen species;VEC. Vascular endothelial cell;VCAM-1. Vascular cell adhesion molecule-1;MCP-1. Monocyte chemoattractant protein-1;TNF- α . Tumor necrosis factor- α ;IL-1 β /6. Interleukin-1 β /6;COX-1/2. Cyclooxygenases-1/2;MAPK. Mitogen-activated protein kinase;TLR-4. Toll-like receptor 4;NF- κ B. Nuclear factor kappa-B;LPS-LBP-CD14. LPS-LBP-CD14 complex

图3 热应激条件下内毒素对畜禽心血管系统的损伤及机制(本图由Figdraw绘制)

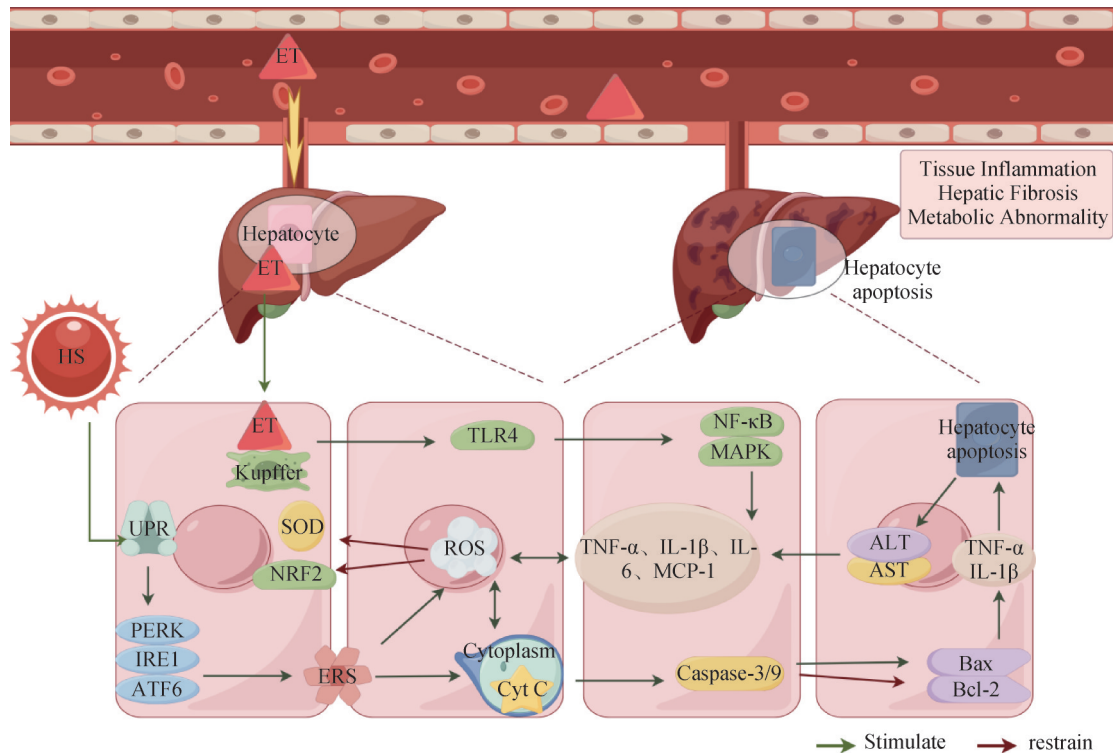
Fig. 3 The damage and mechanism of endotoxin on the cardiovascular system of livestock and poultry under heat stress conditions (by Figdraw)

坏^[56]。ET还可诱导一氧化氮(Nitric oxide, NO)合成,促使枯否细胞(Kupffer)呼吸爆发,释放ROS形成氧化应激^[55](图4)。大量ROS引发膜脂质过氧化,从而破坏细胞膜的完整性导致肝细胞损伤。此外,ET作用于肝细胞后,会促进内皮素-1(Endothelin-1, ET-1)的合成与释放,ET-1对MCP-1的生成具有促进作用,进而使炎症细胞聚集,加剧肝纤维化^[55]。

2.4 对家畜乳腺的损伤及机制

在热应激环境下,ET对家畜乳腺的损伤机制涉及炎症反应、氧化应激及细胞凋亡等多重途径的综合作用,从而导致家畜乳脂率和产量严重下降。ET可激活乳腺上皮细胞(mammary epithelial cell, MEC)表面的TLR4-CD36,触发核因子NF- κ B信

号通路诱导促炎因子(IL-1 β 、IL-6、TNF- α)的大量释放,从而导致乳腺组织炎症损伤^[57-60]。热应激会加剧这一过程,研究表明,热应激可通过抑制机体NRF2通路降低抗氧化酶活性,导致ROS积累引发氧化损伤,这一过程会加剧ET的侵入同时放大炎症反应,最终导致乳屏障关键蛋白ZO-1和Occludin的表达水平显著下降^[61-62]。研究表明,ET刺激奶牛MEC可使细胞膜的渗透性增加,从而促进细胞凋亡^[63]。热应激与ET协同激活线粒体依赖性凋亡通路,上调促凋亡基因Bax、Caspase-3并抑制抗凋亡基因Bcl-2,导致MEC凋亡增加^[61]。热应激通过扰乱内分泌轴和能量代谢,降低乳腺细胞的修复能力,从而加重ET诱导的炎症损伤。热应激和ET的对家畜的损伤导致畜禽产奶性能下降。研究表明,



HS. 热应激; ET. 内毒素; UPR. 未折叠蛋白反应; PERK. 蛋白激酶R样内质网激酶; IRE1. 肌醇需求酶1; ATF6. 活化转录因子6; ERS. 内质网应激; Kupffer. 枯否细胞; NRF2. 核因子E2相关因子2; SOD. 超氧化物歧化酶; Cytoplasm. 细胞质; Cytochrome c. 细胞色素c; MCP-1. 单核细胞趋化蛋白1; Bax. Bcl-2相关X蛋白; Bcl-1. B细胞淋巴瘤1; ROS. 活性氧; Caspase-3/9. 半胱天冬酶-3/9; TNF- α . 肿瘤坏死因子- α ; IL-1 β /6. 白细胞介素-1 β /6; MAPK. 丝裂原活化蛋白激酶; TLR4. Toll受体4; NF- κ B. 核因子 κ B; ALT. 丙氨酸氨基转移酶; AST. 天冬氨酸氨基转移酶; Stimulate. 促进; Restrain. 抑制

HS. Heat stress; ET. Endotoxin; UPR. Unfolded Protein Response; PERK. Protein Kinase R-like endoplasmic reticulum kinase; IRE1. Inositol-requiring enzyme 1; ATF6. Activating transcription factor 6; ERS. Endoplasmic reticulum stress; Kupffer. Kupffer cell; NRF2. Nuclear factor erythroid 2-related factor 2; SOD. Superoxide dismutase; MCP-1. Monocyte chemoattractant protein-1; Bax. Bcl-2-associated X protein; Bcl-1. B-cell lymphoma 1; ROS. Reactive oxygen species; Caspase-3/9. Cysteine-aspartic acid protease-3/9; TNF- α . Tumor necrosis factor- α ; IL-1 β /6. Interleukin-1 β /6; MAPK. Mitogen-activated protein kinase; TLR4. Toll-like receptor 4; NF- κ B. Nuclear factor kappa-B; ALT. Alanine aminotransferase; AST. Aspartate aminotransferase

图4 热应激条件下内毒素对畜禽肝脏的损伤及机制(本图由Figdraw绘制)

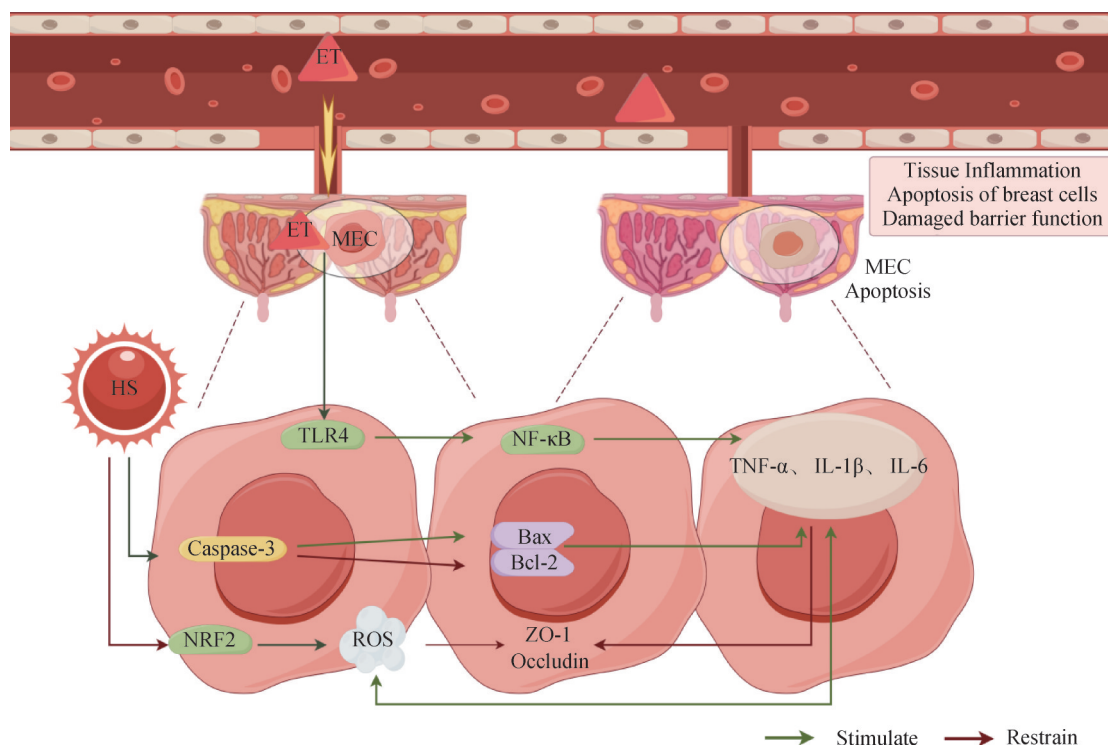
Fig. 4 The damage and mechanism of endotoxin on the liver of livestock and poultry under heat stress conditions (by Figdraw)

ET刺激促进了脂肪酸合酶和乙酰辅酶A羧化酶a基因的表达,长链脂酰辅酶A合成酶1基因表达量呈现下降趋势^[64]。此外,研究还发现微小核糖核酸-29c在ET诱导的炎症中可能通过靶向调控特定基因(PI3K/AKT通路相关因子)参与炎症反应的负反馈调节,但其在热应激下的作用仍需进一步探索^[57]。

2.5 对畜禽生殖器的损伤及机制

在热应激环境下,ET对畜禽睾丸的损伤及其机制主要通过炎症反应、氧化应激和细胞凋亡等多

重途径的综合作用。热应激通过激活下丘脑-垂体-肾上腺轴并抑制下丘脑-垂体-性腺轴,降低促性腺激素和睾酮水平,从而直接抑制精子生成^[65](图6)。在ET进入血液循环后,与睾丸细胞(Testicular cell, TC)表面的TLR4受体结合,激活下游NF- κ B信号通路,促使促炎因子大量表达引发局部炎症反应,进而破坏睾丸屏障^[66]。研究表明,ET作用时间与生殖器功能呈现负相关,具体表现为延长致精子数及活性下降;睾丸生精小管结构紊乱、细胞凋亡;睾丸组织中MDA含量上升、SOD含量下降,氧化应



HS. 热应激;ET. 内毒素;MEC. 乳腺上皮细胞;NRF2. 核因子E2相关因子2;Bax. Bcl-2相关X蛋白;Bcl-1. B细胞淋巴瘤1;ROS. 活性氧;Caspase-3. 半胱天冬酶-3;TNF- α . 肿瘤坏死因子- α ;IL-1 β /6. 白细胞介素-1 β /6;TLR4. Toll受体4;NF- κ B. 核因子 κ B;Stimulate. 抑制;Restraining. 促进

HS. Heat stress; ET. Endotoxin; MEC. Mammary Epithelial Cell; NRF2. Nuclear Factor Erythroid 2-related Factor 2; Bax. Bcl-2-associated X protein; Bcl-1. B-cell Lymphoma 1; ROS. Reactive oxygen species; Caspase-3. Cysteine-aspartic acid protease-3; TNF- α . Tumor necrosis factor- α ; IL-1 β /6. Interleukin-1 β /6; TLR4. Toll-like receptor 4; NF- κ B. Nuclear factor kappa-B

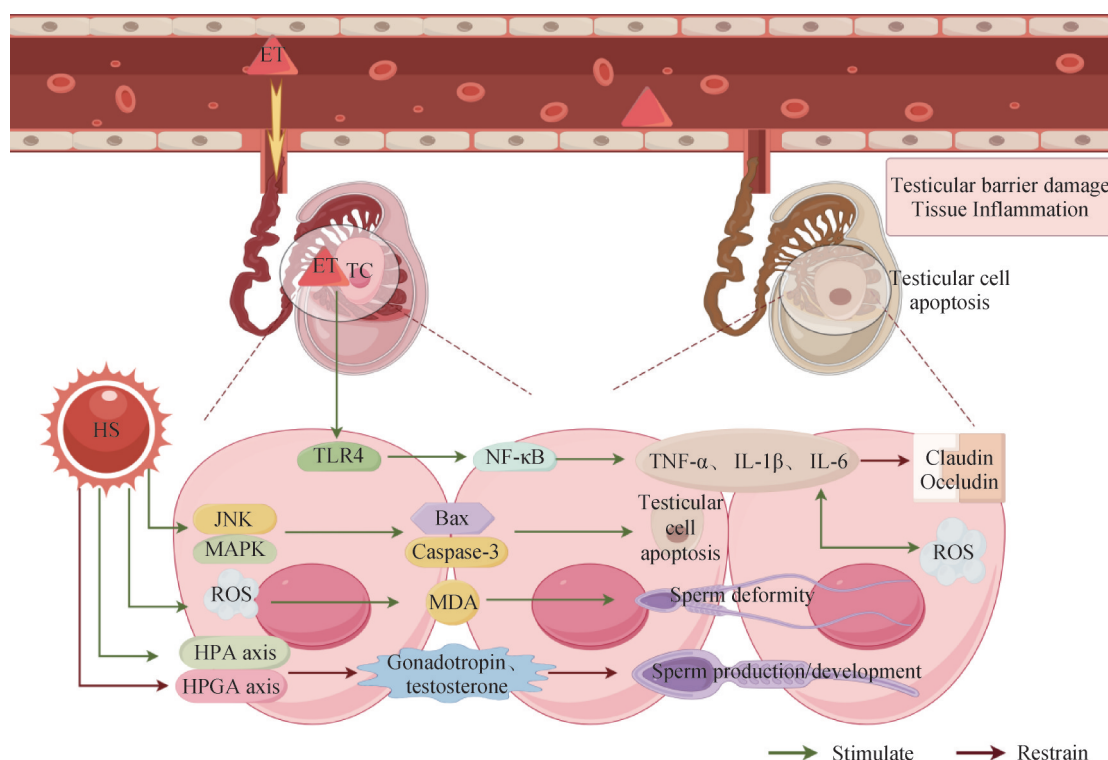
图5 热应激条件下内毒素对家畜乳腺的损伤及机制(本图由Figdraw绘制)

Fig. 5 The damage to the mammary gland of livestock caused by endotoxin and its mechanism under heat stress conditions (by Figdraw)

激严重;睾酮的表达水平逐渐降低^[67](图6)。热应激与ET的协同作用可诱发精母细胞凋亡和精子发生阻滞,研究显示,热应激通过激活c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)和P38 MAPK通路,上调促凋亡基因(*Bax*、*Caspase-3*),同时ET加剧氧化应激,导致线粒体功能障碍和精子细胞膜脂质过氧化,最终表现为精子密度下降和顶体功能缺陷^[68-69](图6)。

热应激与ET对畜禽卵巢的协同损伤作用主要通过炎症反应、氧化应激、激素调节失衡及细胞凋亡等多重机制实现。ET通过结合卵巢颗粒细胞(ovarian granulosa cells, OGCs)上的TLR4激活下游NF- κ B信号通路,诱导促炎因子和ROS的大量分泌^[70]。同时,ET触发NLRP3炎症小体的活化,加剧卵巢局部炎症反应,直接导致卵泡功能障碍和

类固醇激素合成能力下降^[71](图7)。热应激则通过抑制抗氧化酶活性使ROS大量积累直接氧化NLRP3炎症小体加剧炎症反应^[72]。ET与热应激共同作用导致生殖内分泌轴的损伤,热应激通过抑制HPA轴功能从而减少促卵泡素(follicle-stimulating hormone, FSH)和促黄体素(luteinizing hormone, LH)的分泌,而ET可直接作用于OGCs,抑制关键类固醇合成酶的活性,导致雌二醇(estradiol)、孕酮(progesterone)等激素水平下降^[73-76]。热应激通过炎症与氧化应激协同诱导OGCs凋亡,ROS促进促炎因子释放直接激活凋亡通路;同时,ROS过度累积与抗氧化酶活性抑制引发氧化损伤,破坏线粒体功能(*Bax*/*Bcl-2*失衡、*Cyt C*释放),两者协同激活Caspase级联反应,最终OGCs凋亡及卵泡功能衰退(图7)。ET则通过激活AMPK促进OGCs的坏死



HS. 热应激; ET. 内毒素; HPA axis. 下丘脑-垂体-肾上腺轴; HPGA axis. 下丘脑-垂体-性腺轴; JNK. c-Jun 氨基末端激酶; ROS. 活性氧; TC. 睾丸细胞; Gonadotropin. 促性腺激素; Testosterone. 睾酮; MDA. Malondialdehyde; Bax. Bcl-2-associated X protein; Caspase-3. 半胱天冬酶-3; TNF- α . 肿瘤坏死因子- α ; IL-1 β /6. 白细胞介素-1 β /6; MAPK. 丝裂原活化蛋白激酶; TLR4. Toll 受体 4; NF- κ B. 核因子 κ B; Claudin. 紧密连接蛋白; Occludin. 闭合蛋白; Stimulate. 促进; Restrain. 抑制

HS. Heat stress; ET. Endotoxin; HPA axis. Hypothalamic-pituitary-adrenal axis; HPGA axis. Hypothalamic-pituitary-gonadal axis; JNK. C-Jun N-terminal kinase; ROS. Reactive oxygen species; TC. Testicular cell; MDA. Malondialdehyde; Bax. Bcl-2-associated X protein; Caspase-3. Cysteine-aspartic acid protease-3; TNF- α . Tumor necrosis factor- α ; IL-1 β /6. Interleukin-1 β /6; MAPK. Mitogen-activated protein kinase; TLR4. Toll-like receptor 4; NF- κ B. Nuclear factor kappa-B

图 6 热应激条件下内毒素对畜禽睾丸的损伤及机制 (本图由 Figdraw 绘制)

Fig. 6 The damage and mechanism of endotoxins to animal testes under heat stress conditions (by Figdraw)

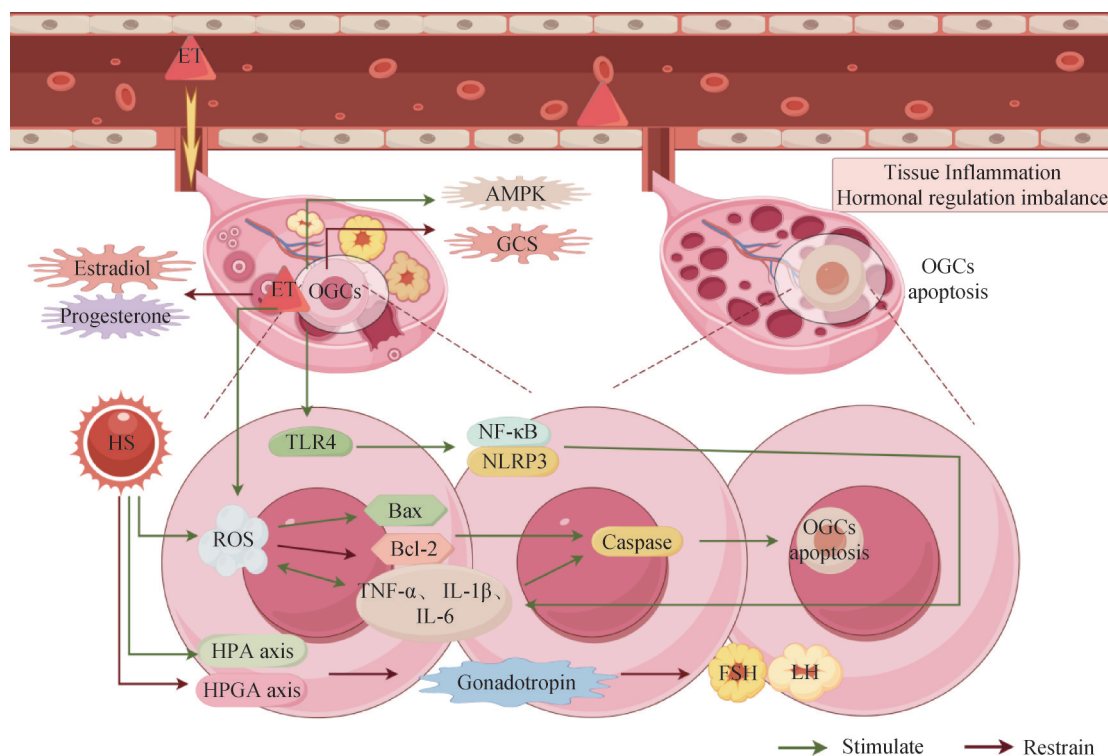
性凋亡^[77]。此外,ET 还能抑制葡萄糖神经酰胺合成酶(Glucosylceramide synthase,GCS)的促凋亡作用,导致卵泡发育停滞^[78]。热应激与 ET 共同作用通过改变卵巢局部免疫微环境干扰免疫-繁殖系统的动态平衡,最终降低生殖性能^[75,79]。

2.6 对畜禽其他脏器的损伤及机制

ET 诱导的内毒血症会增加肾细胞高尔基体磷蛋白(Golgi phosphoprotein 3,GOLPH3)表达,进而诱导高尔基体应激和过量的促炎介质,造成炎症和细胞凋亡^[80]。研究发现,ET 可引起肾小球囊腔变窄、炎性细胞浸润^[81]。随着热应激时间的延长,血清中 ET 含量的不断上升,TLR4 的相对表达量也随之升高,最终导致肾组织、固有细胞因缺血而坏死,且肾损伤程度与热应激持续时间呈正相关^[82-83]。肾缺血致使有害代谢产物不能排出

体外而在体内蓄积,加剧对 ET 对肾功能的损伤^[56,84]。

ET 可损伤肺泡上皮细胞,导致肺泡液体积聚和肺泡气体交换障碍^[85]。研究发现,ET 可通过酪氨酸激酶途径和 PC-PLC 途径激活肺泡巨噬细胞的 NF- κ B^[86]。ET 可激活多形核白细胞(polymorphonuclear leukocyte,PMN)、肺泡巨噬细胞等多种效应细胞和炎症介质,其相互作用放大炎症反应,损伤肺泡细胞,最终导致肺上皮屏障(Alveolar Epithelium Barrier,AEB)损伤,引发肺水肿、肺炎^[85,87-88]。热应激下产生的 ROS 和 ET 与炎性细胞相互作用,产生的 ROS 损伤肺细胞线粒体功能(Bax/Bcl-2 失衡、细胞色素 C 释放),两者协同激活 Caspase 级联反应导致细胞死亡和组织损伤^[89-91]。此外,ET 使纤维蛋白沉积,加重肺损伤。研究发现,ET 作用于炎性细



HS. 热应激;ET. 内毒素;HPA axis. 下丘脑-垂体-肾上腺轴;HPGA axis. 下丘脑-垂体-性腺轴;ROS. 活性氧;Gonadotropin. 促性腺激素;Testosterone. 睾酮;Caspase. 半胱天冬酶;TNF- α . 肿瘤坏死因子- α ;IL-1 β /6. 白细胞介素-1 β /6;TLR4. Toll受体4;NF- κ B. 核因子 κ B;NLRP3. NOD样受体蛋白3;Bax. Bcl-2相关X蛋白;Bcl-1. B细胞淋巴瘤1;FSH. 促卵泡素;LH. 促黄体素;AMPK. 5'-腺苷酸活化蛋白激酶;OGCS. 卵巢颗粒细胞;GCS. 葡萄糖神经酰胺合成酶;Estradiol. 雌二醇;Progesterone. 孕酮;Stimulate. 促进;Restraining. 抑制

HS. Heat stress; ET. Endotoxin; HPA axis. Hypothalamic-pituitary-adrenal axis; HPGA axis. Hypothalamic-pituitary-gonadal axis; ROS. Reactive oxygen species; Caspase. Cysteine-aspartic acid protease; TNF- α . Tumor necrosis factor- α ; IL-1 β /6. Interleukin-1 β /6; TLR4. Toll-like receptor 4; NF- κ B. Nuclear factor kappa-B; NLRP3. NOD-like receptor protein 3; Bax. Bcl-2-associated X protein; Bcl-1. B-cell Lymphoma 1; FSH. Follicle-stimulating hormone; LH. Luteinizing hormone; AMPK. Adenosine monophosphate-activated protein kinase; OGCS. Ovarian granulosa cells; GCS. Glucosylceramide synthase

图7 热应激条件下内毒素对畜禽卵巢的损伤及机制(本图由Figdraw绘制)

Fig. 7 The damage and mechanism of endotoxins to animal ovaries under heat stress conditions (by Figdraw)

胞,使Mnf2蛋白表达下调,成纤维细胞产生胶原蛋白增加^[92-94]。

ET刺激可激活TLR4信号通路,促使脾脏内炎症因子大量表达,并诱导细胞凋亡,最终引发脾损伤^[95-96]。ET刺激可显著上调脾脏TLR4受体mRNA表达水平,进而促使炎症因子表达水平升高^[95,97]。在热应激条件下产生的ROS与炎性细胞相互作用,通过损伤脾细胞线粒体功能,与TLR4通路协同激活Caspase级联反应,加剧细胞程序性细胞死亡。此外,ET可直接刺激脾细胞至脾细胞凋亡,凋亡通路相关因子p53、Bcl-2、Bak和Bax的表达均显著上调^[95]。

3 小结与展望

畜禽在热应激条件下的胃肠道屏障受损和胃肠道菌群紊乱是引发ET累积的主要原因。一方面,热应激诱导胃肠道菌群紊乱促使GNB增殖,增加ET的产生;另一方面,热应激破坏肠上皮紧密连接蛋白表达降低肠道屏障通透性,促使ET入血。ET进入血液循环后主要通过抑制NFR2通路加剧氧化应激,激活TLR4/NF- κ B通路诱导促炎因子的大量释放,最终导致肠道、心血管系统、肝、乳腺和生殖器官等氧化损伤和炎性损伤。为缓解热应激条件下ET对畜禽的损伤,需采取多种干预策略:首

先,可通过添加益生菌、后生元等功能性添加剂调节胃肠道内环境和菌群稳态,减少ET产生;其次,补充营养性添加剂和中草药添加剂修复或强化肠上皮屏障功能,减少ET易位;此外,利用NRF2激活剂增强抗氧化能力、TLR4/NF- κ B抑制剂阻断炎症级联反应,结合日粮营养调控和改善饲养环境等措施,协同消减热应激条件下ET对畜禽机体的损伤。

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