Endotoxin Hazards to Swine and Their Control: Postprint

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Abstract

Endotoxin, also known as lipopolysaccharide, is a component of the cell wall of Gram-negative bacteria that is released during the bacterial growth phase and stationary phase, as well as when bacteria die and lyse. In practical swine production, endotoxins present in the air and feed, as well as disease-induced endotoxins, can all adversely affect pig health and production performance. This article reviews the sources of endotoxin, its effects on pig health and production performance, and control measures for endotoxin, providing a reference for mitigating the hazards of endotoxin in swine production.

Full Text

The Adverse Effects of Endotoxin on Pigs and Its Control

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Abstract: Endotoxin, also known as lipopolysaccharide (LPS), is a component of the cell wall of Gram-negative bacteria that is released during both the growth and stationary phases as well as during bacterial lysis. In practical pig production, endotoxin present in air and feed, along with that induced by disease, can adversely affect pig health and production performance. This paper reviews the sources of endotoxin, its effects on pig health and production performance, and control measures, providing a reference for reducing the harm caused by endotoxin in pig production.

Keywords: pig; endotoxin; source; harm; control

Endotoxin, also called lipopolysaccharide (LPS), is a constituent of the Gram-negative bacterial cell wall that is released during bacterial growth, stationary phase, and upon bacterial death and disintegration [1]. The molecular structure of endotoxin consists of polysaccharide and phospholipid components. The polysaccharide portion comprises the specific O-chain and core region [2]. The specific O-chain, also known as the O antigen, determines the antigenicity of the endotoxin molecule. The core region is divided into outer and inner core areas, with the phospholipid portion connected to the inner core called lipid A, which determines the toxicity of the endotoxin molecule. Endotoxin is heat-resistant and stable; its chemical nature is not protein, and it is not destroyed by heating at 100 ℃ for 1 hour. Its biological activity can only be destroyed by heating at 160 ℃ or higher for 2–4 hours, or by boiling for 30 minutes with strong alkali, strong acid, or strong oxidizing agents. Moreover, endotoxin cannot be converted into toxoid by formaldehyde treatment.

Gram-negative bacteria are ubiquitous in the environment, so endotoxin is present everywhere in soil, air, and water. Additionally, in some large-scale pig farms where bacterial diseases occur year-round, the use of high-dose antibiotics causes Gram-negative bacteria to die and release large amounts of endotoxin [3]. Endotoxin can cause extensive damage to pigs, including fever, septic shock, anorexia, inflammatory responses, tissue injury, and decreased production performance [4]. In recent years, numerous reviews have addressed the effects of endotoxin on ruminants, but few have focused on its hazards to pigs. This paper emphasizes the sources of endotoxin, its effects on pig health and production performance, and control measures to provide a reference for reducing endotoxin harm in pig production.

1 Sources of Endotoxin

1.1 Endotoxin in Barn Air

Air is one of the essential environmental conditions for survival and an important factor affecting pig health in barns. Activities of humans and pigs, among other factors, cause numerous dust particles and microorganisms to float in the air, and endotoxin released by bacteria can exist in the air in a relatively stable form. The concentration of endotoxin in pig barn air is closely related to dust content, and the composition of airborne dust varies considerably, potentially including microbial components and cell wall fragments, dried feces and urine, dander, grain mites, spores, pollen, and particles from feed and bedding [5]. Airborne dust can serve as a carrier for bacterial endotoxin, enabling it to be inhaled deep into the lungs of pigs, thereby causing adverse effects. The concentrations of dust and endotoxin in pig barn air are influenced by activity levels of pigs and humans, mechanical ventilation rates, air humidity, physical characteristics of feed, and type of slatted flooring. Increased activity levels of pigs and humans, higher mechanical ventilation rates, and decreased relative humidity can all elevate airborne endotoxin and dust concentrations [5]. Additionally, barns feeding liquid or pelleted diets have lower dust and endotoxin levels than those feeding meal diets, and barns with plastic slatted floors have lower levels than those with concrete slatted floors [6].

Currently, the threshold concentration of airborne endotoxin that affects pig health is not well understood. One study found that dust concentrations in pig farms in eastern Poland ranged from 3.03-14.05 mg/m^3, with endotoxin concentrations of 1.88–75.0 g/m^3, exceeding the safety threshold (0.1 g/m^3) by 18.8-750 times [6]. Other research indicates that the threshold for airborne endotoxin affecting pig health is 1,540 endotoxin units (EU)/m^3, with most poorly sanitized and environmentally controlled pig barns exceeding this value [7]. Because airborne endotoxin concentrations are greatly affected by environmental conditions, their variation range is large, and the adverse effects of barn air endotoxin on pigs cannot be ignored.

1.2 Endotoxin in Feed

Due to various environmental and production process factors, feed inevitably contains certain amounts of endotoxin [8]. Moreover, an increasing number of feed additives are produced through fermentation by Gram-negative bacteria, particularly *Escherichia coli*, which is widely used in feed additive production. Although *E. coli* K-12 is generally recognized as safe, its endotoxin retains approximately one-quarter of the activity of wild-type strains [9]; therefore, feed additives produced by *E. coli* K-12 may be contaminated with endotoxin, posing potential hazards to animals. Cort et al. [10] reported that the average endotoxin concentration in pig feed was 13 mg/kg, with a maximum concentration of 60 mg/kg. However, evidence suggests that adding high doses of endotoxin to the diet of healthy pigs does not cause clinical symptoms [11]. Studies in mice also found that oral administration of high-dose *E. coli* endotoxin had no significant effect on intestinal structure or cell proliferation [12]. Taniguchi et al. [13] similarly found that oral administration of high-dose single endotoxin had no adverse effects in mice, and no evidence of hepatotoxicity, nephrotoxicity, inflammation, or weight loss was found after 28 days of repeated dosing. Evidently, the intestines of healthy animals can tolerate certain amounts of endotoxin, and the harm caused by oral ingestion of endotoxin in normal, healthy animals is minimal. Therefore, when feeding healthy pigs with feed additives produced by Gram-negative bacteria, if the endotoxin content does not exceed that in normal feed ingredients, pigs will not be significantly affected. However, when pigs experience stress or gastrointestinal dysfunction, their intestinal barrier function decreases, allowing excessive endotoxin from the gastrointestinal tract to enter the body and cause pathological changes [14].

1.3.1 Constipation

Constipation in pregnant sows is a common problem in pig production and represents one of the causes of increased endotoxin entry into pigs. Numerous factors contribute to constipation in pregnant sows, including substantial reductions in daily feed allowance and dietary fiber content, insufficient water intake, heat stress, and lack of exercise [15–16]. Additionally, as the physiological process of parturition approaches, sow intestinal motility decreases, making pre-farrowing sows more susceptible to constipation than pregnant or lactating sows [17]. When sows develop constipation, the intestinal flora undergoes abnormal changes, with *Bacteroides* populations increasing significantly while *Lactobacillus* and *Clostridium* populations decrease markedly, potentially inducing endotoxin production and damage to the intestinal mucosal barrier system. This leads to elevated endotoxin entry into the body, triggering a series of inflammatory responses that can result in death in severe cases [18]. Research also indicates that constipation prolongs feed retention time in the digestive tract, increasing microbial proliferation and endotoxin release and absorption, ultimately leading to postpartum mastitis, metritis, and agalactia [15]. Therefore, constipation is a non-negligible factor contributing to elevated endotoxin levels in pigs.

1.3.2 Diarrhea

Diarrhea is a common disease in piglets, particularly in weaned piglets. The causes of diarrhea in weaned piglets are multifactorial. Early weaning stress causes dramatic changes in intestinal adaptation and impairs digestive function, ultimately leading to diarrhea and even death [19]. Kiers et al. [20] reported that early-weaned piglets have underdeveloped digestive function, low nutrient digestibility, and may develop allergic reactions to dietary antigens, resulting in diarrhea. Li et al. [21] investigated various antinutritional factors in soybean meal (such as trypsin inhibitors, soybean agglutinin, and antigenic proteins) and found these factors could increase intestinal epithelial cell permeability and mucosal edema, accelerate crypt cell growth, and cause villus atrophy and reduced absorptive area, leading to diarrhea. Because piglets have immature thermoregulatory function, inadequate insulation can compromise immunity and cause diarrhea [22]. Diarrhea in piglets leads to congestion, hemorrhage, and edema of intestinal epithelial cells, as well as damage and sloughing of intestinal villi, altering and severely damaging intestinal structure [23]. Concurrently, stress-induced diarrhea causes significant changes in intestinal flora, primarily characterized by decreased populations of beneficial bacteria such as *Lactobacillus* and increased populations of pathogenic bacteria such as *E. coli* [24]. These changes destroy the intestinal microecological barrier, further exacerbating diarrhea. The increased pathogenic microorganisms and compromised intestinal barrier result in elevated endotoxin concentrations in the gut and increased systemic endotoxin entry [25], causing further damage to pigs.

2 Effects of Endotoxin on Pigs

2.1 Effects on the Respiratory System

Airborne endotoxin concentration is closely related to respiratory health status in pigs. Endotoxin in the air can affect the porcine respiratory system to a certain extent. Donham [7] found a correlation between airborne endotoxin concentration and pneumonia, pleurisy, and neonatal piglet mortality in a study of 28 pig farms in southern Sweden. Thorn et al. [26] reported that airborne endotoxin could induce toxic pneumonia. Other studies have shown that dust and endotoxin in pig barns cause respiratory dysfunction and damage to the nasal mucosa [27].

2.2 Effects on Production Performance

After entering the pig’ s body, endotoxin triggers a series of immune responses that ultimately affect production performance. Decreased performance may result from two mechanisms: first, the immune response to endotoxin causes fever and increased pro-inflammatory cytokines, reducing feed intake [28]; second, the endotoxin-induced immune cascade alters metabolic processes, causing nutrients that would otherwise support growth to be reallocated to the immune system, thereby reducing growth rate and feed efficiency [29]. Liu et al. [28] demonstrated that endotoxin-infected pigs showed substantially elevated levels of interleukin (IL)-1β, prostaglandin E2, cortisol, and insulin-like growth factor-1, with average daily gain decreasing by 13% and average daily feed intake decreasing by 12.8%. Chen et al. [30] intramuscularly injected weaned piglets with LPS at a dose of 200 g/kg body weight and found that, compared with the control group, the LPS group exhibited a 28% reduction in average daily feed intake, a 43% reduction in average daily gain, and a 21% reduction in feed conversion efficiency. Endotoxin-induced immune responses alter animal metabolism primarily by affecting protein synthesis and catabolism. Chen et al.’ s [30] nitrogen balance trial also showed that, compared with the control group, the LPS group had a 27% reduction in nitrogen intake, a 45% reduction in nitrogen retention rate, and a 9% reduction in apparent nitrogen digestibility. Research indicates that skeletal muscle protein breakdown rate increases after endotoxin infection, possibly to meet the amino acid requirements for acute-phase protein synthesis [31]. Additionally, inflammatory cytokines induced by endotoxin, such as IL-6, IL-1, and tumor necrosis factor (TNF)-α, can reduce protein synthesis and increase protein breakdown by decreasing the release of anabolic hormones such as growth hormone and insulin-like growth factor and increasing the release of catabolic hormones such as glucocorticoids [32].

2.3 Effects on Renal Na+/K+-ATPase

Pig endotoxin infection triggers a systemic immune response that increases the expression of pro-inflammatory cytokines such as TNF-α, interferon-γ, IL-6, and IL-1 [33]. Inducible nitric oxide synthase (iNOS) is present in renal proximal tubular epithelial cells [34], and these pro-inflammatory cytokines stimulate iNOS expression in renal epithelial cells, leading to nitric oxide (NO) production [35]. NO has vasodilatory effects that can reduce renal blood pressure and glomerular filtration rate [36]. NO and superoxide undergo a biradical addition reaction to produce the strong oxidant peroxynitrite anion (ONOO^-) [37]. Na+/K+-ATPase is highly sensitive to free radicals and membrane lipid peroxidation, and $ONOO^-$ can inhibit its activity by oxidizing sulfhydryl groups at the active site in renal proximal tubules [38]. Additionally, endogenous NO can directly inhibit Na+/K+-ATPase activity in the kidney, causing oxidative damage to proximal tubules and reducing their reabsorptive capacity [39].

3 Control Measures for Endotoxin

3.1 Dephosphorylation of Endotoxin by Intestinal Alkaline Phosphatase

Intestinal alkaline phosphatase (IAP) is an important enzyme located on the apical brush border. During inflammatory responses, epithelial cells can increase IAP expression to modify pro-inflammatory mediators produced by microorganisms. For example, IAP can dephosphorylate endotoxin on the outer membrane of Gram-negative bacteria, thereby reducing its toxicity [40]. Consequently, IAP can inhibit inflammatory cascades in the gastrointestinal tract and suppress bacterial translocation [41]. However, changes in feed palatability and digestibility after weaning reduce feed intake, and alterations in intestinal morphology and physiology decrease IAP activity and expression on the brush border [42]. Some feed additives, such as sodium butyrate and zinc, have been found to promote IAP expression and activation [43]. Prakash et al. [44] demonstrated that sodium butyrate upregulates IAP expression, and Kim et al. [45] reported the role of zinc in promoting IAP expression, suggesting that zinc-induced IAP overexpression may help improve intestinal health. Therefore, adding feed additives such as sodium butyrate and zinc-containing supplements can enhance IAP expression and reduce endotoxin-induced damage.

3.2 Spraying Vegetable Oil to Reduce Airborne Endotoxin

Airborne dust concentration is closely correlated with endotoxin content, and spraying vegetable oil in pig barns can reduce both dust and endotoxin levels. Spraying rapeseed oil in pig barns can reduce total airborne dust by 86% and total airborne endotoxin by 82.5% [46]. Nonnenmann et al. [47] reported that in fattening pig barns sprayed with soybean oil, inhalable dust concentration was 0.65 mg/m^3 compared with 1.39 mg/m^3 in control barns, representing a 54% reduction in inhalable dust and a significant decrease in airborne endotoxin content. However, this method is difficult to promote in practical production due to high economic costs.

3.3 Strengthening Management to Reduce Disease Incidence

Research indicates that heat stress-induced hyperthermia may inhibit the expression of tight junction proteins in intestinal epithelium [48], thereby increasing mucosal permeability and allowing more endotoxin to enter the bloodstream. Therefore, environmental control and sanitation should be strengthened to avoid heat stress and control endotoxin elevation in pigs. Additionally, diseases such as constipation and diarrhea can increase intestinal endotoxin and damage the intestinal mucosal barrier, leading to increased systemic endotoxin entry [18,25]. Thus, maintaining balanced intestinal microflora, enhancing gut health, and reducing the incidence of constipation, diarrhea, and other diseases can effectively control endotoxin levels in pigs.

In summary, factors such as barn environment, feed, and disease can all increase endotoxin levels in pigs. Endotoxin adversely affects the respiratory system, renal Na+/K+-ATPase, and production performance in pigs. A series of measures can be implemented in pig production to reduce endotoxin accumulation, including enhancing intestinal alkaline phosphatase activity, spraying vegetable oil in barns, strengthening management practices, and reducing disease incidence, thereby improving pig health and production performance.

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References:

[1] WELLS J E,RUSSELL J B.The effect of growth and starvation on the lysis of the ruminal cellulolytic bacterium Fibrobacter succinogenes[J].Applied Environmental Microbiology,1996,62(4):1342-1346.
[2] PLAIZIER J C,KHAFIPOUR E,LI S,et al.Subacute ruminal acidosis (SARA),endotoxins and health consequences[J].Animal Feed Science and Technology,2012,172(1/2):9-21.
[3] 王宏艳, 严晗光, 徐玉花. 猪内毒素的综合防治方案研究 [J]. 畜禽业,2015(5):31-32.
[4] WEBEL D M,FINCK B N,BAKER D H,et al.Time course of increased plasma cytokines,cortisol,and urea nitrogen in pigs following intraperitoneal injection of lipopolysaccharide[J].Journal of Animal Science,1997,75(6):1514-1520.
[5] PEDERSEN S,NONNENMANN M,RAUTIAINEN R,et al.Dust in pig buildings[J].Journal of Agricultural Safety and Health,2000,6(4):261-274.
[6] DUTKIEWICZ J,POMORSKI Z J H,SITKOWSKA J,et al.Airborne microorganisms and endotoxin in animal houses[J].Grana,1994,33(2):85-90.
[7] DONHAM K J.Association of environmental air contaminants with disease and productivity in swine[J].American Journal of Veterinary Research,1991,52(10):1723-1730.
[8] LUCHI M,MORRISON D C.Comparable endotoxic properties of lipopolysaccharides are manifest diverse clinical isolates gram-negative bacteria[J].Infection

Immunity,2000,68(4):1899-1904.

[9] SVENSSON M,HAN L,SILFVERSPARRE G,et al.Control of endotoxin release in Escherichia coli fed-batch cultures[J].Bioprocess and Biosystems Engineering,2005,27(2):91-97.

[10] CORT N,FREDRIKSSON G,KINDAHL H,et al.A clinical and endocrine study on the effect of orally administered bacterial endotoxin in adult pigs and goats[J].Journal of Veterinary Medicine: Series A,1990,37(1/2/3/4/5/6/7/8/9/10):130-137.

[11] OKETANI K,INOUE T,MURAKAMI M.Effect of E3040,an inhibitor of 5-lipoxygenase and thromboxane synthase,on rat bowel damage induced by lipopolysaccharide[J].European Journal of Pharmacology,2001,427(2):159-166.

[12] ILLYÉS G,KOVÁCS K,KOCSIS B,et al.Failure of oral E. coli O83 lipopolysaccharide to influence intestinal morphology and cell proliferation in rats:short communication[J].Acta Veterinaria Hungarica,2008,56(1):1-3.

[13] TANIGUCHI Y,YOSHIOKA N,NISHIZAWA T,et al.Utility and safety of LPS-based fermented flour extract as a macrophage activator[J].Anticancer Research,2009,29(3):859-864.

[14] MANI V,HARRIS A J,KEATING A F,et al.Intestinal integrity,endotoxin transport and detoxification in pigs divergently selected for residual feed intake[J].Journal of Animal Science,2013,91(5):2141-2150.

[15] TABELING R,SCHWIER S,KAMPHUES J.Effects of different feeding and housing conditions on dry matter content and consistency of faeces in sows[J].Journal of Animal Physiology and Animal Nutrition,2003,87(3/4):116-121.

[16] PERSSON A,PEDERSEN M A,KUHL W.A long-term study on the health status and performance of sows on different feed allowances during late pregnancy. .Escherichia coli and other bacteria,total cell content,polymorphonuclear leucocytes and pH in colostrum and milk during the first 3 weeks of lactation[J].Acta Veterinaria Scandinavica,1996,37(3):293-313.

[17] KLOPFENSTEIN C,D' ALLAIRE S,MARTINEAU G P.Effect of adaptation to the farrowing crate on water intake of sows[J].Livestock Production Science,1995,43(3):243-252.

[18] FUKUSHIMA S,NIIMI K,TAKAHASHI E.Piebald mutation on a C57BL/6J background[J].Journal of Veterinary Medical Science,2015,77(2):161-166.

[19] ARMSTRONG W D,CLAWSON A J.Nutrition and management of early weaned pigs:effect of increased nutrient concentrations and (or) supplemental liquid feeding[J].Journal of Animal Science,1980,50(3):377-384.

[20] KIERS J L,MEIJER J C,NOUT M J R,et al.Effect of fermented soya beans on diarrhoea and feed efficiency in weaned piglets[J].Journal of Applied Microbiology,2003,95(3):545-552.

[21] LI D F,NELSSEN J L,REDDY P G,et al.Transient hypersensitivity to soybean meal in the early-weaned pig[J].Journal of Animal Science,1990,68(6):1790-1799.

[22] 王红宁. 仔猪腹泻成因及综合防治技术措施 [J]. 中国畜牧杂志,2006,42(6):58-60.

[23] LECCE J G,ARMSTRONG W D,CRAWFORD P C,et al.Nutrition and

management of early weaned piglets:liquid vs dry feeding[J].Journal of Animal Science,1979,48(5):1007-1014.
[24] 左之才, 刘兵, 李莉, 等. 早期断乳应激性腹泻对仔猪肠道形态结构与肠道菌群的影响 [J]. 中国兽医科学,2012,42(1):64-68.
[25] LUDIDI S,JONKERS D,ELAMIN E,et al.The intestinal barrier in irritable bowel syndrome:subtype-specific effects of the systemic compartment in an in vitro model[J].PLoS One,2015,10(5):e0123498.
[26] THORN J,RYLANDER R.Inflammatory response after inhalation of bacterial endotoxin assessed by the induced sputum technique[J].Thorax,1998,53(12):1047-1052.
[27] URBAIN B,MAST J,BEERENS D,et al.Effects of inhalation of dust and endotoxin on respiratory tracts of pigs[J].American Journal of Veterinary Research,1999,60(9):1055-1060.
[28] LIU Y L,LI D F,GONG L M,et al.Effects of fish oil supplementation on the performance and the immunological,adrenal,and somatotropic responses of weaned pigs after an Escherichia coli lipopolysaccharide challenge[J].Journal of Animal Science,2003,81(11):2758-2765.
[29] KLASING K C.Nutritional modulation of resistance to infectious diseases[J].Poultry Science,1998,77(8):1119-1125.
[30] CHEN D W,ZHANG K Y,WU C Y.Influences of lipopolysaccharide-induced immune challenge on performance and whole-body protein turnover in weanling pigs[J].Livestock Science,2008,113(2/3):291-295.
[31] BALLMER P E,MCNURLAN M A,SOUTHORN B G,et al.Effects of human recombinant interleukin-1β on protein synthesis in rat tissues compared with a classical acute-phase reaction induced by turpentine.Rapid response of muscle interleukin-1β[J].Biochemical Journal,1991,279(3):683-688.
[32] HONEGGER J,SPAGNOLI A,D' URSO R,et al.Interleukin-β modulates the acute release of growth hormone-releasing hormone and somatostatin from rat hypothalamus in vitro,whereas tumor necrosis factor and interleukin-6 have no effect[J].Endocrinology,1991,129(3):1275-1282.
[33] GABLER N K,SPURLOCK M E.Integrating the immune system with the regulation of growth and efficiency[J].Journal of Animal Science,2008,86(Suppl.14):E64-E74.
[34] GUZMAN N J,FANG M Z,TANG S S,et al.Autocrine inhibition of Na+/K+-ATPase by nitric oxide in mouse proximal tubule epithelial cells[J].Journal Clinical Investigation,1995,95(5):2083-2088.
[35] MARKEWITZ B A,MICHAEL J R,KOHAN D E.Cytokine-induced expression of a nitric oxide synthase in rat renal tubule cells[J].Journal of Clinical Investigation,1993,91(5):2138-2143.
[36] SCHWARTZ D,MENDONCA M,SCHWARTZ I,et al.Inhibition of constitutive nitric oxide synthase (NOS) by nitric oxide generated by inducible NOS after lipopolysaccharide administration provokes renal dysfunction rats[J].Journal Clinical Investigation,1997,100(2):439-448.
[37] ZHANG C J,WALKER L M,MAYEUX P R,et al.Role of nitric oxide lipopolysaccharide-induced oxidant stress kidney[J].Biochemical Pharmacology,2000,59(2):203-209.

[38] MURIEL P,SANDOVAL G.Nitric oxide and peroxynitrite anion modulate liver plasma membrane fluidity and Na+/K+-ATPase activity[J].Nitric Oxide,2000,4(4):333-342.
[39] KANG D G,KIM J W,LEE J.Effects of nitric oxide synthesis inhibition on the Na,K-ATPase activity in the kidney[J].Pharmacological Research,2000,41(1):121-125.
[40] KOYAMA I,MATSUNAGA T,HARADA T,et al.Alkaline phosphatases reduce toxicity of lipopolysaccharides vitro through dephosphorylation[J].Clinical Biochemistry,2002,35(6):455-461.
[41] VAISHNAVA S,HOOPER L V.Alkaline Phosphatase:keeping the Peace at the Gut Epithelial Surface[J].Cell Host & Microbe,2007,2(6):365-367.
[42] LACKEYRAM D,YANG C B,ARCHBOLD T,et al.Early weaning reduces small intestinal alkaline phosphatase expression in pigs[J].Journal of Nutrition,2010,140(3):461-468.
[43] MALO M S,BISWAS S,ABEDRAPO M A,et al.The pro-inflammatory cytokines,IL-1β and TNF-α,inhibit intestinal alkaline phosphatase expression[J].DNA & Cell Biology,2006,25(12):684-695.
[44] PRAKASH U N S,SRINIVASAN K.Beneficial influence of dietary spices on the ultrastructure and fluidity of intestinal brush border in rats[J].British Journal of Nutrition,2010,104(1):31-39.
[45] KIM J C,HANSEN C F,MULLAN B P,et al.Nutrition and pathology of weaner pigs:nutritional strategies to support barrier function in the gastrointestinal tract[J].Animal Feed Science and Technology,2012,173(1/2):3-16.
[46] SIGGERS J L,KIRYCHUK S P,LEMAY S P,et al.Size distribution of particulate and associated endotoxin and bacteria in traditional swine barn rooms and rooms sprinkled with oil[J].Journal of Agromedicine,2011,16(4):271-279.
[47] NONNENMANN M W,DONHAM K J,RAUTIAINEN R H,et al.Vegetable oil sprinkling as a dust reduction method in swine confinement[J].Journal of Agricultural Safety and Health,2004,10(1):7-15.
[48] 马燕芬，杜瑞平，高民．热应激对奶山羊瘤胃黏膜紧密连接蛋白表达的影响 [J]．动物营养学报,2014,26(3):768-775.

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