Production, Impact, and Prevention and Control Technologies of Endotoxin in Dairy Cattle

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Date: 2017-10-11T00:00:00+00:00

Abstract

Endotoxin, also known as lipopolysaccharide, is a substance released following the death of Gram-negative bacteria or rupture of bacterial cell walls during rapid proliferation. It is ubiquitously present in animal organisms and induces immune stress when present in excess. This article reviews the causes and mechanisms of endotoxin production in dairy cows, its effects on feed intake, blood proteins and amino acids, milk protein and milk fat, strategies for reducing endotoxin load in dairy cows, and provides a reference for mitigating the impact of endotoxins on dairy production.

Full Text

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Abstract: Endotoxin, also known as lipopolysaccharide, is a substance released after the cell wall of Gram-negative bacteria ruptures following bacterial death or rapid proliferation. It is widely present in animal organisms and, when present in excess, causes immune stress in the body. This paper introduces the causes and mechanisms of endotoxin production in dairy cattle, as well as its effects on feed intake, blood proteins, amino acids, milk proteins, and milk fat in dairy cows, and discusses approaches for reducing endotoxin in dairy cattle, providing a reference for reducing the impact of endotoxin on dairy production.

Keywords: endotoxin; mechanism; dairy cattle; ruminal acidosis; prevention and control technology

Chinese Library Classification No.: S823

Ruminal acidosis is one of the common diseases in dairy production, and studies have confirmed that it is closely related to endotoxin. Under normal conditions, endotoxin is commonly present in the rumen and blood of dairy cows; however, because its concentration is relatively low, it does not exert adverse effects on the body. Moreover, endotoxin is also present in the air, feces, and feed of farms. Studies have shown that the endotoxin content in the air of dairy farms can reach as high as 4,243 EU/m3[1-2]. Endotoxin is the strongest inducer of the biological immune system and can induce many cytokines, chemokines, and other inflammatory mediators[3]. Feeding dairy cows high-concentrate diets causes large amounts of volatile fatty acids (volatile fatty acid, VFA) to accumulate in the rumen, resulting in subacute rumen acidosis (subacute rumen acidosis, SARA). At the same time, the pH of rumen fluid in dairy cows decreases, thereby causing Gram-negative bacteria (Gram-negative bacteria, GNB) to rapidly disintegrate in large numbers and release endotoxin[4-5]. Endotoxin is a potent activator of inflammatory responses in many mammalian cells (macrophages, monocytes, endothelial cells, etc.). It induces systemic immune responses and promotes the occurrence of SARA[6]. Endotoxin is highly harmful to dairy cattle; endotoxin entering the body can cause a series of inflammatory reactions in dairy cows. At present, the sites of endotoxin translocation in dairy cattle remain unclear and require further study; thus, it is desirable to block endotoxin translocation to reduce the occurrence of inflammation.

1 Production of Endotoxin in Dairy Cattle and Its Mechanisms of Action

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Date received: 2016-03-21

Funding projects: General Program of the National Natural Science Foundation of China (31372342); National Science and Technology Support Program (2012BAD14B17); Science and Technology Service Network Initiative of the Chinese Academy of Sciences (STS Program) project (KFJ-EW-STS-071)

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1.1 Production of Endotoxin in Dairy Cattle

At present, most dairy farms in China use corn silage and alfalfa as roughage for dairy cattle. To meet the nutritional needs of dairy cows and achieve high milk yield, high-concentrate diets are commonly fed. A diet structure that is high in concentrate and low in roughage can induce abnormal rumen metabolism in dairy cows[7-8]. After large amounts of concentrate are ingested by dairy cows and enter the rumen, abundant carbohydrates are fermented, further producing large quantities of VFAs and organic acids, which causes the pH of rumen fluid to decrease. When pH decreases to 5.2–5.6 for 3–5 h/d, SARA occurs. At the same time, the absorption rate of VFAs decreases in an acidic environment. If pH continues to decline and falls below 5.2, dairy cows develop more severe acute ruminal acidosis (ARA)[9-10]. After ruminal acidosis occurs, large quantities of abnormal metabolic products are produced in the rumen, including endotoxin, lactic acid, histamine, tyramine, ethanol, and others[11-12]. The release of endotoxin in the rumen can be explained as resulting from the death of Gram-negative bacteria caused by the decrease in rumen-fluid pH induced by high-concentrate diets[13-14]. Experiments have shown that, whether in vitro rumen-fluid culture or direct feeding of diets to dairy cows, high-concentrate diets consistently keep the endotoxin content in rumen fluid at a high level, and the dietary concentrate-to-roughage ratio shows a linear increasing relationship with endotoxin content[4-5,11,15-18]. Therefore, the cause of endotoxin production in dairy cows is that, after feeding diets containing large amounts of carbohydrates, rumen microorganisms ferment and produce large quantities of VFAs, leading to a decrease in pH, which in turn induces SARA and releases large amounts of endotoxin.

1.2 Mechanisms by Which Endotoxin Affects Dairy Cattle

The biological effects of endotoxin are not caused by endotoxin itself; rather, after entering the body through the blood circulation, it induces various tissue cells such as lymphocytes and macrophages to release large amounts of inflammatory mediators—including interleukins (IL), tumor necrosis factor (TNF), and coagulation factors—which act on the body and produce a series of responses. Studies have shown that, after ruminal acidosis occurs in dairy cows, the endotoxin among the abnormal metabolic products first enters the blood, then enters the liver through the circulatory system. Kupffer cells in the liver can clear part of the endotoxin[19-20]. However, when large amounts of endotoxin enter the blood, the liver cannot completely clear it, further inducing immune responses in dairy cows[21]. The specific mechanism in the body is that endotoxin first binds to endotoxin-binding protein (LBP), forming an endotoxin-LBP complex. Then, the endotoxin-LBP complex transfers to the CD14 receptor on the cell surface. CD14 mediates recognition of endotoxin by monocytes, macrophages, and other cells, binding to form an endotoxin-LBP-CD14 complex[20,22]. The ternary complex binds to the corresponding receptor Toll-like receptor 4 (TLR4), then activates the nuclear transcription factor κB (NF-κB),

mediating extensive gene expression of pro-inflammatory cytokines and causing inflammatory cytokines (IL-1, IL-6, TNF-α, etc.) to be released, thereby leading the body to produce a series of pathological responses[23-25].

2 Effects of Endotoxin on Feed Intake, Blood Indices, and Milk Components in Dairy Cattle

2.1 Dry Matter Intake (DMI)

Studies have found that the inflammatory response caused by endotoxin can reduce DMI in dairy cows and further lead to a decrease in body weight.

Krajcarski-Hunt et al. [26] showed that healthy dairy cows consumed 25% more total mixed ration (TMR) than cows suffering from SARA. Porter et al. [27] and Oetzel [28] confirmed that endotoxin entering the bloodstream induces immune responses in the body, stimulates the monocyte/macrophage system, and releases inflammatory cytokines such as TNF-α, arachidonic acid metabolites, and histamine. These factors hinder the digestion and absorption of nutrients, causing disturbances in digestive function in dairy cows; they not only reduce feed intake, but also force the body to make extensive use of fat and glycogen, and the two together lead to negative energy balance in dairy cows. Negative energy balance can cause ketosis in dairy cows, and body weight will also continue to decline [29].

2.2 Blood Proteins and Amino Acids

When dairy cows are fed high-concentrate diets and develop SARA, the endotoxin content in rumen fluid increases, and the endotoxin produced can be transported into the blood. Therefore, SARA can significantly increase the endotoxin concentration in peripheral blood [4-5,15]. The endotoxin content in the blood of dairy cows increases with the percentage of concentrate in the diet [30].

With respect to blood proteins, many studies have shown that ruminal acidosis toxicosis can increase the concentrations of acute-phase proteins in the blood, such as C-reactive protein (CRP), haptoglobin (Hp), LBP, and serum amyloid A (SAA) [15-16,31]. It is worth noting that, after endotoxin induces an acute-phase response in the body, blood calcium can stabilize the acute-phase protein structures expressed during the acute-phase response, most prominently stabilizing the structure of SAA. At the same time, blood calcium promotes the aggregation of SAA on tissues and organs, thereby removing part of the endotoxin from the blood [17,32-33]. Zebeli et al. [13] showed that milk fat yield is negatively correlated with CRP content, whereas the endotoxin content in rumen fluid is positively correlated with CRP content. Some researchers believe that this is related to the direct involvement of CRP in lipid and lipoprotein metabolism, and that there is a dose effect [34].

With respect to blood amino acids, the release of endotoxin causes decreases in the concentrations of asparagine (Asn), glutamic acid (Glu), tryptophan

(Trp), methionine (Met), isoleucine (Ile), serine (Ser), lysine (Lys), leucine (Leu), phenylalanine (Phe), glycine (Gly), threonine (Thr), and valine (Val) in the blood, whereas the concentrations of cysteine (Cys), glutamine (Gln), aspartic acid (Asp), and histidine (His) remain essentially unchanged [35-36]. Gln is the first limiting amino acid. Studies in burned mice have shown that when mice develop an immune stress response, energy intake is reduced, leading to breakdown of the body' s own tissues, and Gln content therefore decreases [37]; however, this has not yet been reported in dairy cows. After animals develop an immune response, amino acids in the blood are preferentially used to synthesize acute-phase proteins. Because acute-phase proteins contain relatively large amounts of Trp, Phe, Lys, Ser, and Cys [38], the contents of these amino acids decrease; the decreases in Ile, Leu, and Val may be due to their effects on energy production and antibody formation [39]. Since Thr is a component of immunoglobulins, this may lead to a decrease in Thr content [40]. In summary, endotoxin

Endotoxin induces an immune stress response in dairy cows, leading to an increase in the acute-phase protein content in the blood and a decrease in the content of some amino acids. Because little research has been conducted on the patterns by which endotoxin affects changes in blood amino acid concentrations after SARA occurs in dairy cows, the mechanisms through which endotoxin influences amino acids remain unclear and require further study.

2.3 Milk Fat and Milk Protein

The immune response triggered after endotoxin enters the body can lead to a redistribution of nutrients, causing more nutrients to be used for immune responses and thereby reducing the nutrients entering the mammary gland; consequently, synthesis of milk components in the mammary gland is disrupted[^{41}]. Zebeli et al.[^{13}] found that elevated endotoxin concentrations resulted in decreases in both milk fat percentage and milk fat yield. Waldron et al.[^{42}] confirmed that pro-inflammatory factors induced by endotoxin caused rupture of lysosomes in neutrophils and macrophages, leading to the release of somatic-cell proteases and resulting in degradation of casein in milk. Yuan Lirong[^{43}] showed that different concentrations of endotoxin all significantly reduced the expression of genes related to milk-fat synthesis in mammary tissue of dairy cows, including acetyl-CoA carboxylase-α (*ACACA*), fatty acid synthase (*FASN*), and long-chain acyl-CoA synthetase 3 (*ACSL3*). When the endotoxin concentration reached 10 ng/mL, casein synthesis in mammary tissue was markedly reduced, and endotoxin also significantly decreased the expression of milk-protein genes in mammary tissue of dairy cows, including αS1-casein (*CSN1S1*) and β-casein (*CSN2*). On the one hand, the reduction in milk fat is due to endotoxin stimulating the liver to produce pro-inflammatory factors such as IL-1, IL-6, and TNF-α; these pro-inflammatory factors in turn activate hepatic functional receptors and, through the TLR4 and mitogen-activated protein kinase 1/2 (MEK1/2)–extracellular signal-regulated kinase

1/2 (ERK1/2) pathways, stimulate adipocytes to accelerate lipid hydrolysis and reduce milk-fat synthesis[^{24},^{44}]. On the other hand, endotoxin affects the protein-synthesis pathways mTOR and Janus kinase 2/signal transducer and activator of transcription 5 (JAK2/STAT5), disrupting the amino acids required for milk-protein synthesis and reducing the milk-protein percentage[^{45}]. After SARA occurs in dairy cows, the mechanisms by which endotoxin promotes lipolysis and affects protein pathways have not yet been clearly explained; however, research results indicate that endotoxin increases lipid metabolism in the body to counteract the inflammatory response it induces in dairy cows, ultimately causing decreases in both milk fat percentage and milk protein percentage.

3 Prevention and Control Technologies for Endotoxin in Dairy Cows

3.1 Lactic-Acid-Treated Feed

Because SARA caused by high-concentrate diets leads to the collapse of Gram-negative bacteria and the release of large amounts of endotoxin, the principal approach is to regulate rumen fluid pH in dairy cows and reduce the occurrence of SARA. Studies have shown that lactic-acid treatment is both safe and inexpensive. Lactic acid can alter the structure of starch, making it less readily digested in the rumen. Feeding dairy cows corn that has been soaked in lactic acid shortened the time during which rumen fluid pH was below 5.8 and effectively prevented the development of SARA[^{46}-^{47}]. This treatment involves adding an equal volume of water to the concentrate, soaking it for a period of time in 0.5%–1.0% lactic acid, or heat-treating it at 55 °C for 48 h; thereafter,

formulated as TMR and fed to dairy cows. This method slows the rate of fermentation of grains in the rumen and increases the amount of starch passing through the rumen, thereby reducing ruminal VFA content and maintaining ruminal pH at a relatively high level. Gram-negative bacteria remain relatively stable at a high ruminal pH, and ultimately less endotoxin is produced in the rumen. In addition, a high pH promotes the barrier function of the rumen wall against LPS. This study also indicated that long-term feeding of grains soaked in lactic acid had no adverse effects on dairy cows. Moreover, with lactic-acid-treated feed, even when the concentrate content reached 45% of dry matter, SARA was not induced; on the contrary, milk fat percentage, milk yield, productive life, and other indices of dairy cows were improved.

3.2 Feed Rations Containing Sufficient peNDF

Mertens[^{48}] defined physically effective neutral detergent fiber (peNDF) as neutral detergent fiber (NDF) in the diet that can promote stratification of ruminal liquid and solid phases and influence chewing in ruminants. Shi Renhuang

et al.[^{49}] confirmed that peNDF affects chewing and ruminal buffering in ruminants and is an important factor in stabilizing ruminal pH. Caccamo et al.[^{50}] and Guo Yongqing et al.[^{51}] reported that reducing the proportion of forage in the diet or decreasing forage particle length can reduce peNDF; low peNDF can decrease saliva secretion and the neutralizing capacity in the rumen, shorten rumination time, and ultimately lower ruminal pH, thereby increasing the probability of SARA. To ensure the requirement for dietary peNDF, according to NRC (2001)[^{52}], dairy cow diets should contain at least 25% NDF, of which forage-derived NDF accounts for 75%. Mertens[^{48}] proposed that dietary peNDF for lactating dairy cows should be greater than 15%. Hall et al.[^{53}] showed experimentally that, on a dry-matter basis, feeding efficacy was best when the ratio of starch:soluble fiber:sugars was 40:20:1. Therefore, dairy cows should be fed TMR to ensure the level of peNDF in the diet; sufficient peNDF is conducive to stabilizing ruminal pH, thereby reducing the occurrence of SARA and ultimately affecting the release of endotoxin.

3.3 Other Related Research Progress

Van Vugt et al.[^{54}] showed that monensin changes ruminal pH by influencing the contents of lactic acid and VFA, controls ruminal fermentation, leaves little residue in animals, and has relatively high safety. Adding 30 mg/kg monensin to concentrate can reduce the occurrence of SARA. However, Han Jinshou[^{55}] reported that, while monensin reduces the activity of lactic-acid-producing bacteria, it also lowers the ratio of acetic acid to butyric acid, thereby reducing the precursors for mammary fatty-acid synthesis; therefore, monensin also affects milk fat percentage. McLaughlin et al.[^{56}] and Speight et al.[^{57}] reported that adding acarbose can reduce VFA content, effectively lower lactic acid content in the rumen, and increase ruminal pH. Blanch et al.[^{58}] showed that adding 0.75 g/d acarbose to dairy cow diets can effectively reduce the duration during which ruminal pH is <5.6. Wang Lizhi[^{59}] showed experimentally that supplementing each kilogram of dietary dry matter with 4 g yeast culture and 0.3 g yeast selenium can significantly increase milk yield and milk protein percentage in dairy cows, while reducing blood endotoxin content. Gln is an efficient antioxidant; its metabolite glutathione exerts antioxidant effects. Glutathione can prevent inflammatory mediators from entering the body.

cells, while reducing endotoxin and improving the body' s immunity[^{60}]. A trial involving intraperitoneal injection of Gln in young mice showed that Gln can prevent endotoxin-LBP from forming a complex with CD14, so that NF-κB is not activated, thereby preventing the binding of TLR to endotoxin, inhibiting the synthesis and release of inflammatory mediators, and protecting the intestinal mucosa from injury[^{61}]. However, no reports have yet been found regarding the reduction of endotoxin in dairy cattle. Although the above studies have made efforts to control endotoxin, at present there is no highly practical and effective method for avoiding endotoxin release; further exploration is needed.

4. Conclusion

In summary, endotoxin leads to decreases in feed intake, body weight, milk yield, milk protein percentage, and milk fat percentage in dairy cows. Endotoxin is closely associated with SARA in dairy cows. Although there are not many published reports on acid poisoning in dairy cows and the production of endotoxin in SARA, this disease is widespread and causes enormous losses to the dairy industry. From the available methods for preventing and controlling endotoxin in dairy cows, although trials using lactic-acid-treated feed have produced highly effective results, a large amount of experimental data is still lacking to support them. Therefore, it is necessary to study the pathogenic mechanisms and signaling pathways of endotoxin, prevent endotoxin production at the source, and provide a basis for solving a series of pathophysiological and inflammatory responses caused by endotoxin.

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Endotoxin in Dairy Cattle: Production and Effects and Control Technology

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Abstract: Endotoxin, also known as lipopolysaccharide, is produced when Gram-negative bacteria die or multiply rapidly. It commonly exists in ruminants and results in immunological stress when present in excess. This article elaborates the production and action mechanism of endotoxin in dairy cattle, its effects on feed intake, proteins and amino acids in blood, milk protein and milk fat, and the ways to decrease endotoxin in dairy cattle, which will help reduce endotoxin in dairy-cattle production.

Key words: endotoxin; mechanism; dairy cattle; ruminal acidosis; control technology

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(Responsible editor: WANG Zhihang)

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