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Jugular arginine infusion relieves lipopolysaccharide-triggered inflammatory stress and improves immunity status of lactating dairy cows

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ABSTRACT

The objective of this study was to evaluate the effects of jugular L-Arg infusion on performance and immune function during lipopolysaccharide (LPS)-induced inflammation of lactating dairy cows. Eight Holstein cows (multiparous, 608.8 ± 31.5 kg) at mid-lactation were randomly assigned to 5-d jugular infusions of control (saline), Arg (3 g/h), LPS (0.033 μg/kg per h), and LPS + Arg (0.033 μg/kg per h of LPS and 3 g/h of Arg) in a replicated 4 × 4 Latin square design with 4 infusion periods separated by 10-d noninfusion periods. Jugular solutions of saline, Arg, LPS, and LPS + Arg were continuously infused using peristaltic pumps for approximately 6 h/d during infusion periods. Milk yield was measured on each day of the infusion period. Milk samples were obtained on the last 2 d of each infusion period, and blood samples were obtained on the last day of each infusion period before infusion (0 h) and at 3 and 6 h. We found that the jugular LPS infusion significantly increased serum concentrations of IL-1β, IL-6, tumor necrosis factor, inducible nitric oxide synthase, and lipopolysaccharide binding protein, whereas Arg attenuated the increase in IL-6 and inducible nitric oxide synthase levels and tended to decrease the lipopolysaccharide binding protein level. Arginine alleviated the decrease in dry matter intake and milk fat yield and the increase of somatic cell count induced by LPS. Total casein in milk was decreased during the LPS-induced inflammation period, and jugular Arg infusion significantly increased the content of total casein. In contrast, lactalbumin in milk increased during the LPS-induced inflammation period, whereas jugular Arg infusion significantly decreased the content of lactalbumin. The concentrations of plasma Gly, Thr, Ile, Leu, Arg, Phe, and total free AA were significantly decreased by LPS treatment, but Arg attenuated this tendency. These results indicated that jugular Arg infusion (18 g/d) has protective effects on relieving inflammatory stress and improving immunity status triggered by LPS. In conclusion, Arg could attenuate inflammatory stress and improve milk performance of lactating dairy cows. This protective effect may be due to the ability of Arg to suppress LPS effects and improve immunity status.

Key words: arginine, lipopolysaccharide, inflammatory stress, immunity, dairy cow

INTRODUCTION

High-yielding dairy cattle are often fed concentrate-based diets to meet their energy demands. However, feeding excessively high grain diets increased the concentration of free ruminal LPS due to increased lyses of gram-negative bacteria cells, resulting from a rise in rumen acidity (Khafipour et al., 2009; Plaizier et al., 2012). Extensive research has shown that the LPS accumulation in the rumen can translocate into the peripheral blood circulation (Sato, 2015; Bilal et al., 2016). Once translocated, LPS in blood circulation interacts with lipopolysaccharide binding protein (**LBP**) to augment autologous activity (Plaizier et al., 2012). Subsequently, immunoactivation and systemic inflammatory responses began, after the LPS-LBP complex was transferred to cluster of differentiation 14 (CD14) and recognized by immune cells. This inflammatory response can be experimentally modeled by LPS administration. It has been reported that LPS intravenously infused into systemic circulation was recognized by immune cells, and then elicited the production of inflammation markers such as IL-1, IL-6, tumor necrosis factor (**TNF-α**), and the secretion of acute phase proteins such as LBP in serum (Emmanuel et al., 2008; Ametaj et al., 2010; Zhou et al., 2014). The inflammatory responses induced by LPS markedly disrupted the nutrient metabolism and changed the feed intake behavior in dairy cows (Zebeli and Metzlerzebeli, 2012).

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Kvidera et al. (2017) also reported that intravenously LPS-challenged dairy cows had increased blood glucose consumption by activated immune cells, accompanied by anorexia. During the last decade, extensive research has shown that DMI decreased when dairy cows were given jugular LPS infusion (Waldron et al., 2003; Aditya et al., 2017). In addition, LPS was associated with declines in milk production and quality observed by Dong et al. (2011) and Kobayashi et al. (2013).

Arginine has been shown to be a powerful mediator of multiple metabolic pathways that are vital to inflammation and immune response (Satriano, 2004; Wu, 2013). Arginine is the sole substrate for the production of nitric oxide and the precursor for the synthesis of polyamines, proline, and agmatine, which are important immune modulators. Polyamines are involved in cell division, DNA replication, and regulation of the cell cycle. Proline is responsible for protecting lymphocytes from apoptosis, stimulating cell growth and antibody production. Agmatine can affect the generation and the intracellular concentrations of polyamines. Despite the fact that Arg can be synthesized by the dairy cow, it is normally considered an EAA during inflammatory conditions (Doepel and Lapierre, 2011). In this case, Arg consumption is enhanced, while de novo and exogenous supplies are decreased, as a result of a variety of metabolic and immunologic alterations (Luiking et al., 2009; Wijnands et al., 2015). This evidence may indicate that the inflammation is often associated with Arg deficiency. Therefore, the strategy to supplement Arg has been deemed an effective measure to attenuate inflammatory stress when cows are exposed to a high-grain diet. It has been reported that exogenous administration of L-Arg decreased the production of IL-1β, IL-6, and TNF-α induced by LPS in a rat model (Mohamed et al., 2015). Furthermore, it has been demonstrated that Arg supplementation or intravenous infusion had a positive effect on inflammation and immune response in weaned pigs (Zhu et al., 2013; Pi et al., 2014), broiler chickens (Tan et al., 2014), fish (Jiang et al., 2015), and mice (Calkins et al., 2001). To date, little research has been focused on these potentially protective effects in lactating dairy cows. Our previous in vitro studies showed that Arg effectively attenuated the inflammation induced by LPS in bovine mammary epithelial cells via inhibiting NF-κB signaling pathways (Wu et al., 2016).

Therefore, we hypothesized that Arg could relieve inflammatory stress and improve the immunity status in lactating dairy cows. The objective of the current study was to investigate the effects of Arg on inflammatory responses and production performance, including DMI, milk yield and composition, cytokines, inducible nitric oxide synthase (**iNOS**), LBP, serum metabolite profiles, and the plasma amino acid profiles in lactating dairy cows experimentally challenged with LPS.

MATERIALS AND METHODS

Animals and Housing

All experimental animals received care according to the Guide for the Care and Use of Laboratory Animals by the Chinese Academy of Sciences (2013). Holstein cows at mid lactation (multiparous), averaging 201 DIM and 608.8 kg of BW, were used for this study. Cows were housed in a freestall barn with constant access to water and feed. A common TMR (Table 1) was mixed at 0800 h and offered daily during 15-d periods. Cows were fed ad libitum to achieve a minimum of 5% refusals on as-fed basis. Diets were formulated to meet all nutrient requirements for a 600-kg Holstein cow producing 20 kg of milk containing 4.0% milk fat and 3.0% milk protein as evaluated according to NRC (2001). The daily feed intake of each cow was individually measured throughout the experimental periods. Cows were milked twice daily at 0530 and 1730 h.

Table 1. Ingredients, chemical composition, and nutrient contents of the experimental diets

Item (% of DM, unless noted)	Value
Ingredient	
Chinese wildrye hay	8.50
Alfalfa hay	15.30
Corn silage	31.20
Corn	20.50
Cottonseed meal	2.00
Soybean meal	11.47
DDGS[1]	9.40
NaCl	1.10
Premix[2]	0.50
Total	100.00
Nutrient level[3]	
NE_L (Mcal/kg)	1.61
CP	14.96
NDF	32.27
ADF	20.14
NFC	30.99
Ether extract	3.02
Ash	8.60
Ca	0.90
P	0.61
Concentrate:forage	45:55
NFC/NDF	0.96

[1]DDGS = distillers dried grains with solubles.

[2]One kilogram of premix contains the following: Cu, 3,125 mg; Fe, 5,500 mg; Mn, 4,980 mg; Zn, 17,500 mg; Co, 6.2 mg; I, 6.25 mg; vitamin A, 1,500,000 IU; vitamin D, 31,250,000 IU; vitamin E_3, 125 mg; niacin, 4,500 mg; and choline, 125,000 mg.

[3]NE_L and NFC were calculated in reference to NRC (2001), whereas the other nutrition levels were measured values.