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Effect of non-encapsulated and encapsulated active dried yeast on blood cell count, blood metabolites and immune response of finishing beef heifers☆

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Abstract: A study was conducted to evaluate whether encapsulated active dried yeast (EDY), compared with non-protected (ADY) or antibiotics (ANT), improved immune response and blood metabolites of finishing beef heifers. Blood urea nitrogen was lower ($P < 0.05$) with supplemented ADY and mixture of ADY and EDY (MDY) compared with control. Supplementation of MDY mixture also resulted in lower ($P < 0.05$) red blood cell distribution width than control. Lipopolysaccharide binding protein was less ($P < 0.05$) for EDY than control, ANT and ADY as well as cytokine concentration of interleukin-6 was less ($P < 0.05$) for MDY versus control.

Keywords: blood metabolites, immune response, beef heifers, encapsulated active dried yeast

Introduction

High-grain diets are commonly used in North American feedlot operations to meet energy requirements of high-producing cattle. However, feeding high-grain diets usually results in rapid accumulation of fermentation acids in the rumen following feed ingestion and can lead to various metabolic disorders, including subacute rumen acidosis, liver abscesses and lameness (NASEM 2016). Low ruminal pH is often associated with an increased release of toxins (lipopolysaccharides; LPS) from bacteria in the rumen and gut, which subsequently induces inflammatory responses (Plaizier et al. 2012). The LPS can stimulate the release of pro-inflammatory cytokines and acute phase proteins in blood (Tian et al. 2019). Inflammation can suppress immune responses and set the stage for disease. Antibiotic growth promoters (AGP) are currently used to control gastrointestinal dysfunction and improve growth

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performance. However, increasing concerns over the use of AGP in animal production has prompted the need to develop natural alternatives.

Active dried yeast (ADY; commonly *Saccharomyces cerevisiae*) mainly consists of live yeast cells (>10 billion cfu g^{-1}). Feeding ADY to ruminants has been shown to exert numerous beneficial effects on rumen fermentation and nutrient digestibility (McAllister et al. 2011). Recently, several studies from our group demonstrated beneficial activities in the intestine by feeding beef cattle ruminally protected ADY. Jiao et al. (2017) reported that supplemental ruminally protected ADY improved digestibility of fibre and protein in the intestine and total digestive tract of beef cattle. Ran et al. (2018) reported increased concentrations of blood urea N and glucose and reduced fecal *Escherichia coli* counts in beef cattle supplemented with protected ADY, suggesting possible anti-pathogenic activity of ADY in the lower gut. Additionally, the mannans and glucans in yeast cell wall have been shown to provide animal health and growth performance benefits (Shurson, 2018). These polysaccharide components decrease colonization of pathogens in the gastrointestinal tract and help modulate immune activity, resulting in an improvement in animal health (Spring et al. 2015). Consistently, feeding protected or non-protected yeast fermentation products (different from ADY) to finishing cattle has reported increased fecal IgA concentration (Shen et al. 2018), and increased blood acute phase protein concentrations (Shen et al. 2019), indicating improved immune responses.

Thus, we hypothesized that feeding ADY or protected ADY would alter blood metabolites associated with improved nutrient digestibility and enhance beneficial

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effects on immune response of beef cattle fed a high concentrate diet. The objective of this study was to investigate the effects of ADY and rumen protected ADY on blood metabolites and immunity of beef heifers fed a high grain diet. The results for feed intake, ruminal pH and fermentation, and site and extent of feed digestion in the digestive tract of finishing beef heifers were reported previously (Jiao et al. 2017).

Materials and methods

Animals, design, yeast sample preparation and diets

Experimental procedures involving animals received approval from the institutional Animal Care and Use Committee and animals were cared for according to the guidelines of the Canadian Council on Animal Care (2009). The ADY (1.71×10^{10} cfu g^{-1}; *Saccharomyces cerevisiae*, Biomate®) was provided by AB Vista (Marlborough, Wiltshire, UK) and the number of viable ADY cells was confirmed using a spreading plate method (Jiao et al. 2017). Animal management, experimental design and procedures were previously described in detail (Jiao et al. 2017). In brief, five ruminally cannulated Angus beef heifers (average body weight of 650 ± 48.8 kg) were used in a 5 × 5 Latin square design with five 21-d periods including 14 d of adaptation and 7 d of sampling. Each period was followed by a 7-d washout period to minimize carryover effects. The five treatments were: 1) control (no ADY, monensin or tylosin); 2) antibiotics (ANT; 110 mg tylosin and 300 mg monensin $heifer^{-1}$ d^{-1}); 3) ADY (1.5 g ADY $heifer^{-1}$ d^{-1}); 4) encapsulated ADY (EDY; 3.5 g EDY $heifer^{-1}$ d^{-1}); and 5) a mixture of ADY and EDY (MDY; 1.5 g ADY and 3.5 g EDY $heifer^{-1}$ d^{-1}). The EDY consisted of 1.5 g ADY (1.71×10^{10} cfu g^{-1}) and 2 g capsule materials

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(barley hordein and glutelin), and was prepared using a micro-encapsulation technique (Jiao et al. 2017). The treatment mixture of ADY and EDY was expected to have both effects on rumen fermentation and postruminal activity and was compared with ADY or EDY alone. The heifers were fed a total mixed ration ad libitum once daily and gradually transitioned to a high grain diet over 4 wk. The diet consisted of 10% barley silage, 20% corn dried distillers grain with solubles, 67% dry-rolled barley grain, and 3% mineral and vitamin supplement (dry matter [DM] basis). The chemical composition of the dietary DM was 95.3% organic matter, 27.4% neutral detergent fibre, 10.4% acid detergent fibre, 38.3% starch, and 17.9% crude protein (Jiao et al. 2017). Ground barley grain (100 g) was evenly mixed with each treatment and delivered to heifers by top-dressing onto the ration twice daily at 0900 h and 1700 h, respectively.

Blood sampling and analysis

On d 16 and 21 of each period, blood samples were taken from the jugular vein of each heifer 2 h after feeding. Three 10 mL vacuum tubes with Na heparin, with no additive or with K_2EDTA were used, respectively, to collect plasma, serum or to measure hematological parameters (Vacutainer, Becton Dickinson, Franklin Lakes, NJ, USA). The samples were centrifuged at 3000 × g at 4°C for 20 min to obtain supernatants of plasma and serum, and then the collected plasma and serum samples were frozen at -20°C until analyzed.

The hematological parameters were measured using a fully automatic Hematology Analyzer (MEK-6318K, Nihon-Kohden, Tokyo, Japan), including red

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blood cells (RBC), mean corpuscular volume (MCV), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC distribution width (RDW), RBC distribution width absolute (RDWa), platelet count (PLT), mean platelet volume (MPV), hemoglobin concentration (HGB), white blood cells (WBC), lymphocytes, monocytes and granulocytes. A subsample (1 mL) of the plasma was centrifuged at 16000 × g for 2 min at 4°C to remove fibrinogen, and a dry chemistry analyzer (VetTest analyzer, model 8008, IDEXX Lab, Westbrook, ME, USA) was used to analyze the blood glucose and blood urea N (BUN). A commercially available enzymatic colorimetric procedure was used to analyze serum nonesterified fatty acids (NEFA; NEFA-HR 2, Wako Chemicals Inc., Richmond, VA, USA). Bovine ELISA kits (Cloud-Clone Corp., Katy, TX, USA) were used to determine the concentrations of serum amyloid A (SAA). All samples including standards were tested in duplicate. Samples were initially diluted 1:500. Optical density values was read on a microplate spectrophotometer (MRX Microplate Reader, Dynatech Laboratories, Chantilly, VA) at 450 nm. Concentrations of plasma haptoglobin (Hp) were determined using bovine ELISA kits (Tridelta Development Ltd.) with a pool of bovine serum as the standard. Optical density values were read on the MRX Microplate Reader (Dynatech Laboratories) at 630 nm. Concentrations of lipopolysaccharide binding protein (LBP) were determined with ELISA kit that cross-reacts with bovine LBP (Cell Sciences Inc., Norwood, MA, USA). Plasma samples were initially diluted 1:1,500, and samples with optical density values less than the range of the standard curve were diluted 1:1,200 and assayed according to the

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manufacturer's instructions. The optical density at 450 nm was measured using a microplate spectrophotometer (model Spectra Max 190, Molecular Devices Corporation, Sunnyvale, CA). The concentration of LBP was calculated from a standard curve of known amounts of human LBP. Plasma IL-1, IL-6 and IL-10 were determined using bovine ELISA kits (Cusabio Biotech, Newark, NJ, USA). Duplicates were conducted for each sample including the standards, and a microplate reader (Bio-Rad, xMarkTM, USA) was used to read the optical density values at 450 nm. The intra- and inter-assay coefficient of variations for Hp, SAA, LBP, IL-1, IL-6 and IL-10 were all below 10%.

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Statistical analyses

Data were analyzed using the Mixed procedure of SAS (SAS Inst. Inc., Cary, NC) for a 5 × 5 Latin square design. Fixed effect of treatment and random effects of heifer and period were included in the mixed model. Sampling day was considered a repeated measure for variables measured over time. For repeated measures, various covariance structures were tested with the final choice exhibiting the lowest value for Akaike's information criteria. LSMEANS included the Tukey correction used to adjust the PDIFF option statement to account for multiple comparisons among treatments. Differences between treatments were declared significant at $P \leq 0.05$, and trends were discussed at $0.05 < P \leq 0.10$.

Results

Heifers supplemented with ADY and MDY had lower ($P < 0.05$) concentration of BUN than control heifers (Table 1). Hematological parameters did not differ among

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treatments except that supplementation of ADY and MDY had less ($P = 0.04$) RDW than control.

Blood WBC, lymphocytes, monocytes and granulocytes did not differ among treatments (Table 2). Plasma Hp and serum SAA concentrations were not affected whereas, plasma LBP concentration was less ($P < 0.05$) for EDY than control, ANT or ADY, and it tended ($P < 0.10$) to be less with MDY than control. Plasma concentrations of IL-1 and IL-10 were not affected by treatments, but IL-6 concentration was less ($P < 0.05$) with MDY or tended ($P < 0.10$) to be less for EDY than control.

Discussion

Decreased BUN concentration with ADY and MDY is consistent with the report of Ding et al. (2008), that the addition of ADY reduced BUN concentrations of lambs. Decreased BUN concentration with ADY and MDY along with greater protein digestibility in the total digestive tract observed previously (Jiao et al. 2017), suggest an improvement of protein efficiency by feeding ADY alone or with MDY. The reduction of LBP and IL-6 concentration by feeding either EDY or MDY (both included rumen protected ADY) suggests a post-ruminal effect of ADY on immune response. Ran et al. (2018) suggested that feeding rumen protected ADY to cattle fed high-grain diets may reduce translocation of LPS through the hindgut into the bloodstream. Shen et al. (2018) reported greater fecal IgA concentration with duodenal delivery of yeast culture compared with control heifers not receiving yeast or heifers receiving yeast orally, and suggested an improvement of intestinal mucosal

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immunity with post-ruminal yeast supplementation. Additionally, RDW is a possible surrogate biomarker of inflammation and has a clinical importance in disease diagnosis (Horta-Baas and Romero-Figueroa 2019). Therefore, reduced concentrations of RDW, LBP and IL-6 with supplementation of rumen protected ADY (EDY and MDY) might have resulted from an improvement in intestinal immunity or reduced LPS translocation into the blood stream of beef heifers (Ran et al. 2020).

Monensin provides benefits to ruminants in terms of feed efficiency, growth performance, and reduction in the occurrence of subclinical diseases (Drong et al. 2016). In the current study, lack of effect of ANT on blood metabolites and hematological parameters may be due to the previously reported lack of differences in DM intake, nutrient digestibility, ruminal pH and fermentation parameters between control and ANT (Jiao et al. 2017). Contreras et al. (2018) suggested that supplementation of monensin had beneficial effects on immunity of ruminants due to a greater availability of glucose that is used for anaerobic glycolysis by the immune cells, thereby improving phagocytosis and killing activity. In the present study, feeding monensin to heifers did not affect blood glucose concentration compared with control or yeast, which may account for the lack of effect on blood immune response. Moreover, the immune response seemed to be more pronounced with rumen protected ADY (i.e., EDY and MDY), which likely had greater activity in the intestine. A limited amount of monensin was expected to reach the intestine as most monensin fed to animals is absorbed from the rumen and metabolized in the liver (Herberg et al.

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1978). In agreement with the current study, Drong et al. (2016) found that supplementation of monensin had no effects on WBC, lymphocytes, monocytes or granulocytes compared with control in dairy cows. In addition, blood immunity, and the dominant phylum and genus of ruminal bacteria were not different with supplemented monensin compared with control in fattening lambs (Jia et al. 2018).

Conclusion

Supplementation of ADY lowered BUN of beef heifers fed a high-grain diet, suggesting improved protein utilization. The reduction of plasma LBP and IL-6 concentrations indicated less acute phase protein response, suggesting a possible decrease of LPS translocation from hindgut or improved intestinal immunity by feeding rumen protected ADY. Feeding ANT to finishing beef heifers did not show beneficial effects on blood metabolites or immune response. These results suggest that supplemented rumen protected ADY may lower the need for an immune response, and thus potentially improved energy use efficiency.

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Table 1. Effects of antibiotics (ANT), active dried yeast (ADY), encapsulated ADY (EDY) and a mixture of ADY and EDY (MDY) on blood metabolites and parameters of beef cattle.

	Treatments						
Item[a]	Control	ANT	ADY	EDY	MDY	SEM	P-value
Blood metabolites							
Glucose, mg dL^{-1}	72.7	74.4	71.6	74.4	75.5	1.76	0.30
BUN, mg dL^{-1}	20.4^{a}	19.5^{ab}	18.4^{b}	19.2^{ab}	18.2^{b}	1.29	0.04
NEFA, mmol L^{-1}	0.10	0.11	0.12	0.11	0.11	0.016	0.80
RBC, $\times 10^6$ μL^{-1}	6.89	6.78	6.83	6.82	6.82	0.188	0.97
MCV, fl	53.1	53.1	53.6	53.2	53.2	1.05	0.34
HCT, %	36.5	35.9	36.6	36.3	36.3	0.84	0.94
MCH, pg	19.6	19.6	19.7	19.8	19.6	0.36	0.78
MCHC, g dL^{-1}	36.9	37.0	36.7	37.1	36.9	0.28	0.41
RDW, %	23.7^{a}	23.6^{ab}	23.2^{bc}	23.6^{ab}	23.0^{c}	0.88	0.04
RDWa, fl	43.0	43.1	42.8	42.5	43.4	1.86	0.51
PLT, $\times 10^3$ μL^{-1}	307	293	327	285	309	16.8	0.17
MPV, fl	5.9	6.1	6.1	6.1	6.0	0.14	0.23
HGB, g dL^{-1}	13.5	13.3	13.4	13.5	13.4	0.29	0.94

Note: Means within a row with different superscripts differ ($P < 0.05$).

[a]BUN = blood urea N; NEFA = nonesterified fatty acid; RBC = red blood cell; MCV = mean corpuscular volume (fl = femtoliters); HCT = hematocrit; MCH = mean corpuscular hemoglobin (pg = pictograms $cell^{-1}$); MCHC = mean corpuscular hemoglobin concentration; RDW = red blood cell distribution width; RDWa = red blood cell distribution width absolute; PLT = platelet count; MPV = mean platelet volume; HGB = hemoglobin concentration.

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Table 2. Effects of antibiotics (ANT), active dried yeast (ADY), encapsulated ADY (EDY) and a mixture of ADY and EDY (MDY) on blood immunity of beef cattle.

	Treatments						
Item[a]	Control	ANT	ADY	EDY	MDY	SEM	P-value
WBC, × 10^3 μL^{-1}	8.7	8.4	8.1	8.7	8.6	0.56	0.76
Lymphocytes, ×10^3 μL^{-1}	4.1	4.1	4.1	4.0	4.0	0.38	0.98
Lymphocytes, %	48.7	49.6	50.4	48.2	47.8	4.71	0.77
Monocytes, ×10^3 μL^{-1}	0.77	0.76	0.68	0.78	0.77	0.063	0.19
Monocytes, %	8.2	8.5	8.1	8.6	8.4	0.35	0.74
Granulocytes, ×$10^3$$\mu L^{-1}$	3.8	3.5	3.4	3.9	3.8	0.62	0.38
Granulocytes, %	43.1	42.0	41.5	43.2	43.8	4.64	0.80
Acute phase proteins							
Hp, µg mL^{-1}	1089	1467	1116	1085	1204	181.9	0.36
SAA, µg mL^{-1}	156	151	145	143	147	11.7	0.92
LBP, µg mL^{-1}	4.9^{a}	4.8^{a}	4.4^{a}	2.8^{b}	3.6^{ab}	0.48	0.03
Cytokine concentrations							
IL-1, pg mL^{-1}	522	537	570	532	533	23.3	0.26
IL-6, pg mL^{-1}	413^{a}	344^{ab}	349^{ab}	342^{ab}	275^{b}	29.9	0.05
IL-10, pg mL^{-1}	546	447	443	499	495	52.7	0.63

Note: Means within a row with different superscripts differ ($P < 0.05$).

[a]WBC = white blood cells; Hp = haptoglobin; SAA = serum amyloid A; LBP = lipopolysaccharide binding protein; IL-1 = interleukin-1; IL-6 = interleukin-6; IL-10 = interleukin-10.

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