Original Article

The effects of maternal supplementation of rumen-protected lysine during the close-up dry period on newborn metabolism and growth in Holstein calves

Running title: Effects of lysine supply in late-gestation on calf growth

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Acknowledgments

The authors would like to thank Miss Yuka Tanimura, Aki Taniguchi, Yuka Yajima, and Haruka Yamaguchi (Obihiro University, Japan) for supporting our research, and Mr. Yusuke Sugimoto (Ajinomoto Co., Inc.) for technical support with amino acid analyses.

Abstract

This study aimed to evaluate the effects of rumen-protected lysine (RPL) supplementation during the close-up period on blood metabolites and calf growth. Forty multiparous Holstein dams were selected based on parity, body condition score, and expected calving date, and randomly assigned to a group: with RPL (n = 22) or without (CON, n = 18). RPL dams were supplied daily with 80 g of RPL from day 21 before the expected calving date to parturition. Blood samples were obtained from the dams before the start of supplementation, one week before calving, and immediately after calving, and from calves immediately after birth and weekly until 8 weeks of age. Body weight measurements were performed immediately after birth in all calves and at weekly intervals until 8 weeks of age in female calves. No significant difference was observed in serum metabolite levels and plasma amino acid concentrations between the RPL and CON dams before supplementation, whereas plasma lysine concentrations tended to be higher in RPL dams immediately after calving ($p = 0.07$). Serum total protein levels ($p < 0.05$) were higher, whereas plasma total amino acid, total essential amino acid, total non-essential amino acid, and other amino acid concentrations were lower in the calves of RPL dams than those of CON dams ($p < 0.05$). There were no significant differences in calf birth weight between the two groups, although female calves of RPL dams (n = 7) had higher serum total protein ($p < 0.05$) and tended to have greater body weight ($p = 0.09$) from 1–8 weeks of age than those of CON dams (n = 11). Overall, RPL supplementation during the close-up period may increase placenta-mediated amino acid transfer to the fetus and enhance protein synthesis in the calf, leading to improved weight gain during the suckling period.

Keywords: *close-up dry period, Holstein cattle, metabolism, newborn calf, rumen-protected lysine*

1. Introduction

Glucose and amino acids are the main nutrients required for fetal growth (Bell & Ehrhardt, 2002; Nishida, 2009). Reduced insulin sensitivity in peripheral tissues during late gestation, an insulin-independent process, ensures adequate transfer of glucose from the dam to the fetus (Hayirli, 2006). Although placental glucose transfer is dependent on maternal–fetal plasma glucose concentration gradient, it is also influenced by other factors, including glucose transporters, maternal nutrition, and fetal growth capacity (Bell & Ehrhardt, 2002). Conversely, most amino acids are transported against a fetal–maternal concentration gradient via active transport processes (Bell & Ehrhardt, 2002). In a previous study on ewes, short-term fasting during late gestation showed no significant effects on the umbilical net uptake of amino acids, despite appreciable decreases in the maternal plasma concentrations of many amino acids (Lemons & Schreiner, 1983). This study concluded that the supply of amino acids from the dam to the fetus does not change dramatically during maternal fasting. Alternatively, Kwon et al. (2004) showed that long-term maternal nutrient restriction in ewes reduces blood amino acid concentrations in both fetuses and umbilical veins. Moreover, maternal malnutrition during gestation is related to retarded development of both the uterus and fetus and overdevelopment of placenta in beef cattle (Micke et al., 2010; Rasby et al., 1990).

Lysine is usually a limiting amino acid in dairy cows fed forage- and corn-based feed. The recommended amount of metabolizable lysine during the close-up dry period is 90–95 g/d from the point of view of postpartum milk protein yield (French, 2016). Dairy cows supplemented with rumen-protected lysine (RPL) during the close-up period show increased intake of dry matter in the peripartum period and improved lipid metabolism after calving (Girma et al., 2019), as well as increased yield of energy-corrected milk and milk protein (Fehlberg et al., 2020). Therefore, it is clear that lysine supplementation in dairy cows during the close-up period improves their performance during the peripartum period; however, there is still little research on the effect of maternal supplementation with RPL during the close-up dry period on the growth and metabolism of their fetuses and calves. To the best of our knowledge, there is only one study on this topic, which showed that the maternal supplementation with RPM or RPL or the two combination during the close-up period enhanced the passive immunity and growth of their calves (Wang et al., 2021). Moreover, some studies have shown that the calves born to Holstein dams supplemented with methionine, another limiting amino acid in dairy cows (NRC, 2001), during late pregnancy exhibited enhanced growth (Alharthi et al., 2018; Batistel et al., 2019). As a matter of course, methionine and lysine have different roles because methionine is a glucogenic amino acid (that can be converted into glucose through gluconeogenesis) while lysine is a ketogenic amino acid (that can be degraded directly into acetyl-CoA); however, we hypothesized that maternal supplementation of RPL during late gestation may increase the supply of amino acids to fetus, increased protein synthesis in the liver and contribute to fetal development and calf growth after birth. Therefore, the present study investigated the effects of RPL supplementation during the close-up period on calf growth and concentrations of blood metabolites and amino acids.

2. Materials and Methods

2.1 Animals, feeding, and management

The experiment was conducted at the Field Center of Animal Science and Agriculture, Obihiro University of Agriculture and Veterinary Medicine. We examined 40 multiparous Holstein cows that calved between December 2018 and October 2019, and their calves. The cows were moved to a paddock for the close-up dry period at approximately one month before the expected calving date. During the close-up dry period, all cows were fed once daily with a limited total mixed ration (11.3 kg DM/cow/d) consisting of grass silage, corn silage, and dry cow concentrate. In addition, grass hay, minerals, and water were available ad libitum. Additional dry cow concentrate rations were offered using the feeding station, depending on the number of days before the expected calving date (day −15 to −11: 0.5 kg/cow/d; day −10 to −6: 1.0 kg/cow/d; day −5 to calving: 1.5 kg/cow/d). Diets were formulated using AMTS.Cattle.Pro version 4.16 (AMTS LLC, USA). The cows were selected based on parity, body condition score (BCS), and expected calving date, and randomly assigned to one of the two experimental diets: with RPL or without. Twenty-two cows (RPL group) were orally administered 80 g of RPL (AjiPro®-L, Ajinomoto Health & Nutrition North America, Inc., USA) and 30 g of rice bran daily from day 21 before the expected calving date to parturition. Eighteen cows (CON group) were orally administered 30 g of rice bran daily during the same period. Parity and BCS at the initiation of experiment in the RPL and CON groups were 1.7 ± 0.2 and 1.9 ± 0.3 (p = 0.557), and 3.47 ± 0.06 and 3.40 ± 0.08 (p = 0.605), respectively. The estimated dietary metabolizable lysine intake based on AMTS software for RPL and CON diet was 95.4 and 75.4 g/d for the RPL and CON diet, respectively. Calving difficulty was recorded for all the cows.

The calves were separated from the dams immediately after birth and fed twice with colostrum on the first day. For the first feeding, the female calves were fed colostrum with a density higher than 1,042 kg/m^3 or 750 g of colostrum replacer powder (Headstart®, Elanco Japan Co., Ltd., Tokyo, Japan) mixed with water and all male calves were fed 750 g colostrum replacer powder (Headstart®) mixed with water until up to 5–6 hours after birth. The colostrum of individual cows was stored at −20 °C, and thawed with warm water before feeding. For the second feeding, the calves were fed 750 g of colostrum replacer powder (Headstart®) until up to 12 h after birth. From day 2 to 7 after birth, the calves were fed twice daily with 2 L of milk replacer (150 g/L of Calftop EX, National Federation of Dairy Cooperative Associations, Tokyo, Japan; TDN >103%, CP >28%, crude fat >15%). From day 8 after birth, male calves were sold, and female calves were moved to an automatic calf feeder. The amount of milk replacer fed to the calves was gradually increased until it reached a maximum of 6 L/d, which was then maintained until the end of the experiment.

2.2 Sampling

During the experimental period, corn silage, grass silage, and hay were collected monthly and stored at −30 °C for chemical composition analysis. The same operator also assessed the BCS at the initiation of the study using a 1 to 5 scale, with increments of 0.25 units, according to Ferguson et al. (1994). Blood samples of dams were obtained via caudal venipuncture twice weekly, beginning from the onset of supplementation (day 21 before expected calving) to calving day (immediately after calving). In addition, colostrum was collected from the dams immediately after calving by hand milking, of which 5 mL from each dam was frozen at −30 °C until analysis for immunoglobulin G (IgG). Blood samples of calves were collected from the jugular veins immediately after birth and before the first colostrum feeding. The calves were cleaned and dried with a towel and weighed before the first colostrum feeding. The amount of colostrum intake during the first and second feeding was also recorded. In addition, the female calves were subjected to weekly blood sampling and body weight and height measurements until up to eight weeks of age. Non-heparinized, silicone-coated 9 mL tubes (Venoject, Autosep, Gel + Clot. Act., VP-AS109K; Terumo Corporation, Tokyo, Japan) were used for total protein, albumin, glucose, and gamma-glutamyl transpeptidase (GGT) analyses, and 5 mL tubes containing ethylenediaminetetraacetic acid (Venoject II, VP-NA050K; Terumo Corporation, Tokyo, Japan) were used for amino acid analysis. To obtain serum, blood samples were allowed to coagulate for 10 min at 38 °C in an incubator. All tubes were then centrifuged at 2,328 × *g* for 15 min at 4 °C, and serum and plasma samples were stored at −30 °C and −80 °C until being subjected to glucose and total protein analyses, and amino acid analyses, respectively.

2.3 Measurement of feed, blood, and colostrum samples

The chemical composition of corn silage, grass silage, and hay was determined using near-infrared reflectance spectroscopy (National Federation of Dairy Cooperative Associations, Tokyo, Japan). The serum concentrations of glucose and total protein were measured before supplementation, one week before the expected calving date, and immediately after calving in dams, and immediately after birth in calves using a clinical chemistry automated analyzer (TBA120FR; Toshiba Medical Systems Co., Ltd., Tochigi, Japan). Serum total protein, albumin, glucose, and GGT levels were also measured in female calves until up to 8 weeks of age using the clinical chemistry automated analyzer (TBA120FR). The plasma concentrations of amino acids of dams and calves were measured at the indicated times using an ultra-performance liquid chromatography–MS (Waters, Milford, MA, USA), with the derivatization method (AccQ-Tag Derivatization) provided by Waters. Colostrum IgG concentrations were measured using bovine single radial immunodiffusion test kits (Mitsumaru Chemical Co., Ltd., Miyagi, Japan).

2.4 Statistical analysis

Data from a male calf in the CON group immediately after birth were excluded from the analysis because the calf was fed a small amount of colostrum before blood collection. The period of 0–6 days after birth was regarded as 0 weeks of age. Serum total protein, albumin, glucose, and GGT levels, and body weight and height measurements of female calves for 1–8 weeks of age were analyzed using repeated-measures analysis of variance (ANOVA; SigmaPlot® 13; Systat Software, Inc., San Jose, CA, USA), which included the time (week of age), group, and individual calves as subjects of repeated measurements. When the interaction between group and time was significant ($p < 0.05$), all pairwise multiple comparisons at each time point were performed using the post hoc Holm–Šidák test (SigmaPlot). The calf sex ratio of each group and the occurrence of diarrhea in female calves were analyzed using the chi-squared test. Other data were analyzed using Student's *t*-test or the Mann–Whitney U test after statistical testing for normality using the Shapiro–Wilk test (SigmaPlot). Results are reported as the mean ± standard error of the mean. Statistical significance was set at $p < 0.05$, and the tendency was considered from $p > 0.05$ to $p \leq 0.10$.

3. Results

Table 1 shows the actual ingredients and nutrient composition of the diets provided to the dams during the close-up dry period. The actual amount of metabolizable lysine in the RPL and CON groups was lower than the estimated amount.

The blood parameters of dams before supplementation, one week before the expected date of calving, and immediately after calving, are shown in Figure 1. Table 2 shows the supplemental period, calving difficulty, sex of calves, calf body weight at birth, colostrum IgG concentration of dams. The amounts of first colostrum and IgG intake that affect growth and occurrence of diarrhea during the suckling period in female calves of the RPL and CON groups are shown in Table 2. There were no significant differences between the blood parameters of RPL and CON groups at the initiation of the experiment (Figure 1). Plasma isoleucine concentrations tended to be higher in the RPL group compared with the CON group ($p = 0.089$) at one week before calving day; however, there were no significant differences between the other parameters of the two groups (Figure 1). The duration of experimental diet supplementation of the RPL group was shorter than that of the CON group ($p = 0.003$, Table 2). Sex and body weight of the calves at birth were similar in both groups, and calving difficulty was not significantly different between the groups (Table 2). Colostrum IgG concentrations of dams were 120.7 and 108.7 mg/mL in the RPL and CON groups, respectively; however, there was no significant difference between the two groups (Table 2). Immediately after calving, the plasma glycine concentration ($p = 0.033$) of dams in the RPL group was higher, and plasma isoleucine ($p = 0.063$) and lysine ($p = 0.069$) concentrations tended to be higher, whereas plasma aspartic acid ($p = 0.092$) tended to be lower compared with those of the CON group (Figure 1). The other blood parameters were not significantly different between the two groups (Figure 1). The colostrum intake of female calves during the first feeding after birth was 2.0 L in both groups (Table 2). The IgG concentrations of the first colostrum fed to female calves were similar, and the IgG intake of female calves was not significantly different between the RPL and CON groups (Table 2).

Table 3 shows the blood parameters of all calves of the RPL and CON group immediately after birth. Immediately after birth, the serum total protein concentration of calves in the RPL group was higher than that of the calves in the CON group ($p = 0.046$, Table 3). In contrast, plasma total amino acid ($p = 0.010$), total essential amino acid ($p = 0.017$), total non-essential amino acid ($p = 0.018$), threonine ($p = 0.035$), phenylalanine ($p = 0.017$), methionine ($p = 0.001$), arginine ($p = 0.003$), asparagine ($p = 0.049$), serine ($p = 0.014$), glutamic acid ($p = 0.008$), alanine ($p = 0.004$), glycine ($p = 0.049$) and proline ($p = 0.003$) concentrations were lower while plasma aspartic acid ($p = 0.056$) tended to be lower in the calves of the RPL group than in those of the CON group (Table 3). There were no significant differences in the other blood parameters between calves of the RPL and CON groups immediately after birth (Table 3).

Body weight, body height, and blood parameters of female calves at 1–8 weeks of age are presented in Figure 2. Serum total protein concentrations were higher ($p = 0.024$) while serum albumin concentrations ($p = 0.065$) and body weight ($p = 0.092$) tended to be higher in the female calves of the RPL group than in those of the CON group, at 1–8 weeks of age (Figure 2). In addition, the occurrence of diarrhea in the female calves of the CON group (63.6%, 7/11) tended to be higher than that in the female calves of the RPL group (14.3%, 1/7) during the first eight weeks after birth ($p = 0.066$). The other parameters did not differ significantly between the two groups (Figure 2).

4. Discussion

In this study, the plasma concentrations of most of the amino acids in the dams of the RPL group were similar to those in the CON group, although plasma lysine concentrations immediately after calving tended to be higher in the dams of the RPL group. In a relatively similar study, dairy cows supplemented with RPL and rumen-protected methionine (RPM) for three weeks before calving tended to have higher plasma lysine concentrations and significantly higher plasma branched-chain amino acid and total essential amino acid concentrations compared with those of the control group, at three days before the expected calving date (Lee et al., 2019). The amount of metabolizable lysine was 61 g/d in cows supplemented with RPL and RPM and 53 g/d in the cows of the control group (Lee et al., 2019). Lee et al. (2019) indicated that the rate of catabolism and transamination of lysine may increase when the amino acid supply exceeds the demands of cows. However, in another study, in which dairy cows were supplemented with RPL (metabolizable lysine; 98 g/d vs. 80 g/d in control) for four weeks before calving, plasma lysine concentrations were higher while most other amino acid concentrations were lower in the cows supplemented with RPL than in the cows of the control group (Fehlberg et al., 2020); this shows that the increase in lysine concentrations in plasma can be attributed to increased lysine supply while the decrease in plasma concentrations of other amino acids is likely due to the increased ability to use almost all amino acids owing to increased duodenal supply of lysine.

French (2016) recommended an amount of 90–95 g/d of metabolizable lysine during the close-up dry period from the point of view of postpartum milk protein yield. In the present study, the actual amount of metabolizable lysine was lower than the amount recommended by French (2016), although the amount of estimated metabolizable lysine before the onset of the experiment was more than 95 g/d. In addition, the dams of the present study were fed grass and corn silage-based diets, which have a low lysine content (NRC, 2001), and were not fed soybean meal. Additionally, even the cows supplied with RPL in this study may not have received an adequate amount of lysine because they gave birth earlier than the expected calving date, and hence, the supplemental period was shorter than three weeks. Therefore, although the plasma lysine concentration increased slightly, the amount of RPL supplementation in our study might not have been enough to increase the catabolism and transamination of lysine and the utilization of other amino acids, and hence, the plasma concentration of other amino acids did not show any changes.

Moreover, Batistel et al. (2017) showed that the mRNA expression of several uteroplacental transporters of amino acids and glucose increases in late-gestation dairy cows supplied with methionine. Although lysine was not supplied in the study mentioned above, its supply to dams during late gestation might alter the nutritional transfer to the fetus. The plasma amino acid concentrations of dams supplied with lysine were similar to those of the control group in this study, which can be attributed to their increased utilization for protein and non-essential amino acid synthesis for colostrum synthesis in the mammary gland (Lapierre et al., 2009), as well as the increased supply of amino acids to the fetus. Therefore, further research is needed to study the changes in placental clearance and transport systems of amino acids, and protein and amino acid composition in the colostrum of dams supplied with lysine.

Although there is still little research on the effects of maternal supplementation with RPL during the close-up dry period on growth and metabolism of their fetuses and calves; however, Wang et al. (2021) showed that the maternal supplementation with RPL for 21 days before calving enhanced the plasma IgG concentrations, serum total protein concentration and daily gain until weaning of their calves. However, RPM supplementation in late-pregnant dams resulted in increased mRNA expression of several uteroplacental transporters of amino acids and glucose (Batistel et al. 2017) and changes related to maturation of the metabolic pathways in the liver (Jacometo et al., 2017; Jacometo et al., 2016) and immune function (Alharthi et al., 2019; Jacometo et al., 2018) in their calves. In another study, in which RPM was supplied to transition dairy cows for 4 weeks before calving, plasma amino acid concentrations (e.g., histidine, lysine, methionine) and plasma urea concentrations at birth were significantly lower and higher (not significantly), respectively, in the calves of dams supplied with RPM than in the calves of control dams (Alharthi et al., 2018). In addition, increased of supply of amino acids to the mesenteric vein in cows enhances protein synthesis within the liver (Wray-Cahen et al., 1997). Therefore, it can be considered that calves born from dams supplied with RPL may have higher placenta-mediated amino acid transfer and higher protein synthesis in the liver, thereby resulting in higher serum total protein concentrations and lower plasma amino acid concentrations immediately after birth.

During the first nine weeks of life, the body weight and average daily gain in calves of dams supplied with RPM for four weeks before calving were significantly greater than in calves of dams fed the control diet under conditions where there was no difference in colostrum and IgG concentration in colostrum between the two groups, although body weight at birth differed between the calves of RPM (44.1 kg) and control (42.1 kg) dams (Alharthi et al., 2018). In addition, although body weight at birth in female calves of dams supplied with RPM for four weeks before calving was similar to that in calves of the control dams, body weight, hip height, and wither height in female calves of dams supplied with RPM were higher than those in the calves of control dams, during the first nine weeks of life (Batistel et al., 2019). As mentioned previously, RPM supplementation in late-pregnant dams induced the maturation of metabolic pathways in the liver of their calves (Jacometo et al., 2017; Jacometo et al., 2016). In the present study, the female calves of RPL dams showed greater body weight and higher serum total protein and albumin concentrations during 1 to 8 weeks of age. Since the serum glucose concentration and GGT activity reflect the energy status (Chilliard et al., 1998; Kida, 2002) and IgG intake from the colostrum and the failure of passive transfer (Elitok, 2018; Topal et al., 2018), respectively, the energy status and transfer of passive immunity were similar between the calves of the two groups. However, the occurrence of diarrhea in female calves of the CON group tended to be higher. Calves with diarrhea show lower blood albumin levels (Choi et al., 2021), which might explain the lower serum albumin concentrations in female calves of the CON group. In addition, the higher serum total protein concentrations in female calves of the RPL group may indicate higher liver function and immune function, similar to the results of previously reported studies on RPL or RPM supplementation (Alharthi et al., 2019; Jacometo et al., 2018; Jacometo et al., 2017; Jacometo et al., 2016; Wang et al., 2021). We did not measure the plasma IgG concentrations in calves; however, a previous study has shown that calves from dams supplied with RPL during the close-up period have enhanced plasma IgG concentrations and serum total protein concentrations (Wang et al., 2021). Therefore, the female calves of the RPL group in the present study may have higher IgG concentrations in blood and as a result, the occurrence of diarrhea may have been reduced. Furthermore, maternal supplementation with RPL during late gestation may promote the maturation of liver function during the fetal period and improve postnatal growth. The limitations of this study are: i) the actual amount of metabolizable lysine was lower than the recommended amount and ii) the supplemental period was shorter than the predetermined three weeks because the cows gave birth earlier than the expected calving date. Hence, further research is needed to clarify this.

In conclusion, our data indicate that maternal supplementation of RPL during the close-up period may increase placenta-mediated amino acid transfer to the fetus and enhance protein synthesis in the fetus and calf after birth, leading to improved weight gain during the suckling period.

Conflict of interest

The authors declare no conflict of interest for this article.

Animal Welfare Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to, and that the appropriate ethical review committee approval has been received. The experimental procedures performed in the present study complied with the Guide for the Care and Use of Agricultural Animals of Obihiro University (approval number: #18-181, 19-91 and 20-53).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (Chiho Kawashima, Ph. D.) upon reasonable request.

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Figure Legends

Figure 1.

Serum glucose, total protein, and plasma amino acid concentrations in dams before supplementation, one week before calving day (−1 wk), and immediately after calving. The numbers of RPL and CON dams were 22 and 18, respectively. Values are presented as mean ± standard error of the mean.

Figure 2.

Body weight, body height, and serum total protein, albumin, glucose, and gamma-glutamyl transpeptidase (GGT) levels in female calves of RPL and CON groups, at 1–8 weeks of age. The numbers of female calves of RPL and CON dams were 7 and 11, respectively. Values are presented as mean ± standard error of the mean. *P*-values indicate significant differences during the 1–8 weeks of age between the two groups.