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Intramammary administration of lipopolysaccharides at parturition enhances immunoglobulin concentration in goat colostrum

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ABSTRACT

In newborn ruminants, transfer of passive immunity is essential to obtain protection against pathogens. This study aimed to increase the permeability of the blood-milk barrier using intramammary lipopolysaccharides (**LPS**) in goats at parturition to modulate colostrum composition. Twenty multiparous *Majorera* dairy goats were randomly allocated in one of the two experimental groups. The LPS group (n = 10) received an intramammary administration (**IA**) of saline (2 mL) containing 50 μg of LPS from *Escherichia coli* (O55:B5) in each half udder at parturition. The control group (n = 10) received an IA of saline (2 mL). Rectal temperature (**RT**) was recorded, and a blood sample was collected at parturition (before IA). In addition, RT was measured, and blood and colostrum/milk samples were collected on day (d) 0.125 (3 hours), 0.5 (12 hours), 1, 2, 4, 7, 15 and 30 relative to the IA. Goat plasma immunoglobulin G (**IgG**) and M (**IgM**) and serum β-hydroxybutyrate, glucose, calcium, free fatty acids, lactate dehydrogenase and total protein concentrations were determined. Colostrum and milk yields as well as chemical composition, somatic cell count (**SCC**), IgG and IgM concentrations were measured. The MIXED procedure (SAS 9.4) was used, and the model included the IA, time, and the interaction between both fixed effects. Statistical significance was set as $P < 0.05$. Goats from the LPS group showed higher RT on d 0.125, 0.5 and 4 relative to the IA compared to the control group ($P_{IA \times Time} = 0.007$). Goat serum biochemical variables and plasma IgG and IgM concentrations were not affected by the IA. Colostrum and milk yield as well as chemical composition were not affected by the IA, except for milk lactose percentage that was lower in the LPS group compared to the control group (4.3 ± 0.08 and 4.6 ± 0.08%, respectively $P_{IA} = 0.026$). Colostrum SCC was higher in the LPS group than in the control group (3.5 ± 0.09 and 3.1 ± 0.09 cells × 10^6/mL, respectively; $P_{IA} = 0.011$). Similarly, milk SCC increased in the LPS group compared to the control group ($P_{IA} = 0.004$). The LPS group showed higher IgG ($P_{IA} = 0.044$) and IgM ($P_{IA} = 0.037$) concentrations on colostrum than the control group (31.9 ± 4.8 and 19.0 ± 4.8 mg/mL, 0.8 ± 0.08 and 0.5 ± 0.08 mg/mL, respectively). No differences in milk IgG and IgM concentrations between groups were observed. In conclusion, the IA of LPS at parturition increases RT, SCC and IgG and IgM concentrations in colostrum without affecting either yield or chemical composition.

Implications

Dairy goat industry faces important losses caused by high perinatal mortality. Therefore, providing good quality colostrum to goat kids is essential. This study offers a novel and unique approach to improve colostrum quality, based on the application of intramammary lipopolysaccharides at parturition. This strategy can increase immune components (i.e., immunoglobulins) in colostrum, and consequently enhance the performance and immune status of goat kids during the first weeks of life, reducing the incidence of transfer of passive immunity failure and the use of antibiotics, which has a positive effect on animal welfare and the economic benefit of producers.

Introduction

Mammals have developed different strategies to provide immunity to their offspring. In ruminants, due to the placental structure,

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the transfer of passive immunity strictly depends on early colostrum intake after birth to provide immunization until newborns are able to synthesize their own immune components (Castro et al., 2005). Colostrum contains a complex mixture of bioactive molecules (Barrington et al., 2001; Hernández-Castellano et al., 2014), with immunoglobulin G (**IgG**) the most abundant (McGrath et al., 2015; Puppel et al., 2019).

In the mammary gland, the blood-milk barrier is responsible for preventing an indiscriminate exchange of components between blood and milk. Although, colostrum synthesis is mostly based on active mechanisms such as endocytosis or transcytosis, immune components such as IgG can be also transferred into colostrum through leaky tight junctions (Baumrucker and Bruckmaier, 2014; Hernández-Castellano et al., 2018). During mastitis (i.e., inflammation of the mammary gland), the tight junctions between epithelial mammary cells are damaged and the integrity of the blood-milk barrier is reduced, increasing the passage of plasma proteins, antibodies, and leukocytes among others from blood to milk (Nguyen and Neville, 1998; Bruckmaier and Wellnitz, 2017).

Reduced integrity of the blood-milk barrier has been used to study the inflammatory response of the udder under different challenges (Wellnitz et al., 2011; Vernay et al., 2012; Wall et al., 2018). In dairy cows, the intramammary administration of oxytocin (Wall et al., 2016a), progesterone (Nguyen and Neville, 1998) and some nonsteroidal anti-inflammatory drugs such as selective and not selective cyclooxygenase (Sintes et al., 2020) reduce the integrity of the blood-milk barrier, whereas prolactin (Flint and Gardner, 1994) and glucocorticoids such as cortisol (Herve et al., 2017) or prednisolone (Wellnitz et al., 2014) stabilize it preventing leakage.

Lipopolysaccharides (**LPS**) are cell wall components of Gram-negative bacteria that play an important role in host–pathogen interactions with the innate immune system (Maldonado et al., 2016). The intramammary administration (**IA**) of LPS can mimic a sterile mastitis, and indirectly, modifies colostrum and milk composition (González-Cabrera et al., 2022). This study hypothesizes that the IA of LPS at parturition increases the permeability of the blood-milk barrier, enhancing the transfer of immune components, such as IgG, from blood to colostrum and milk. Therefore, this study aimed to use an IA of LPS at parturition to improve colostrum and milk composition in dairy goats.

Material and methods

Experimental design

The present experiment was carried out on an experimental farm located in the Veterinary Faculty at the Universidad de Las Palmas de Gran Canaria (Arucas, Spain).

Twenty pregnant *Majorera* dairy goats within the second and fourth lactation with an average BW 65.7 ± 2.80 kg were used in this study. All animals were visually healthy before they were included in the experiment. From the fourth month of gestation to the first month of lactation, animals were fed according to the guidelines published by *L'Institut National de la Recherche Agronomique* (Sauvant et al., 2018) and had free access to water and to mineral blocks (i.e., Na, 36.0 g/kg; Ca, 1.00 g/kg; Mg, 0.6 g/kg; $MnSO_4$, 312 mg/kg $FeSO_4$, 200 mg/kg; Na_2SeO_3, 33 mg/kg; Ca (IO_3), 24 mg/kg; $(CH_3COO)_2Co^*4H_2O$, 8 mg/kg). Feed composition during late gestation (i.e., fourth and fifth month) and first month of lactation is described in Table 1.

The experimental period started at parturition and lasted until week 4 postpartum. At parturition, each goat was randomly allocated to one of the two experimental groups. Goat kids were immediately removed after birth and were not allowed to suck colostrum from the dams. The LPS group (n = 10) received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5, Sigma-Aldrich, St. Louis, MO) diluted in 2 mL of saline solution 0.9% in each half udder immediately after parturition and 3 hours (h) before first milking, and therefore in full udders. Similarly, goats from the control group (n = 10) received an IA with 2 mL of 0.9% saline solution in each half udder without LPS. Teat openings were disinfected with 70% ethanol, and then, a 1.0 × 130 mm sterile catheter (Buster Cat Catheter, Kruuse, Norway) was used for the IA.

Table 1
Feed composition of the diets used daily during late gestation (i.e., fourth and fifth month) and first month of lactation in the experimental goats.

Item	Gestation		Lactation
	4th month	5th month	1st month
Ingredients, kg (DM basis)			
Maize	0.69	0.65	0.65
Soybean meal (oil < 5%, 46% protein + oil)	–	–	0.13
Lucerne dehydrated (16–18% protein)	–	–	0.18
Italian ryegrass hay	0.60	0.68	0.60
Lucerne hay	–	–	0.43
Nutrients (DM basis)			
Gross energy, kcal	5 612.3	5 783.2	8 678.5
CP, g	102.5	104.5	266.9
Crude fat, g	224.4	252.8	431.1
NDF, g	487.3	539.2	814.6
Starch, g	510.2	478.3	492.8
Calcium, g	2.9	3.3	12.7
Phosphorous, g	7.5	7.3	9.5

Blood, colostrum, and milk sampling

Blood samples were collected immediately after parturition and before the IA (0 h) and then on day (d) 0.125 (3 h), 0.5 (12 h), 1, 2, 4, 7, 15 and 30 relative to parturition. Samples were collected from the jugular vein using 20 mL syringes (Injekt Braun, Braun, Germany) and 20G needles (Sterican Braun, Braun, Germany). Blood was immediately transferred to EDTA-K2 tubes (BD Vacutainer®, UK) for plasma collection, and serum tubes (SEROTUB, Deltalab™, Spain). Plasma tubes were placed on wet ice immediately after collection and centrifuged at 2 190 × *g* for 5 min at 4 °C (Hettich-Zentrifugen, Universal 32 R, Tuttlingen, Germany) within 30 minutes. Serum tubes were stored at room temperature for 2 h and then centrifuged at 2 190 × *g* for 5 min at 4 °C. Both plasma and serum were aliquoted in 1.5 mL Eppendorf Tubes®.

Colostrum and milk samples were collected on d 0.125, 0.5, 1, 2, 4, 7, 15 and 30 postpartum. Goats were milked completely in a double 12-stall parallel milking parlour (Alfa Laval Iberia SA, Madrid, Spain) equipped with recording jars (3.5 L ± 5%) using the procedure described by Torres et al. (2013).

All samples (i.e., plasma, serum, colostrum, and milk) were stored at −20 °C until laboratory analyses were performed.

Variables

Immunoglobulin G (IgG) and M (**IgM**) concentrations in blood plasma, colostrum and milk were measured using commercial ELISA kits (Bethyl Laboratories, Montgomery, TX, USA). The intra-assay coefficients of variation were 5.8 and 4.8%, respectively. The inter-assay coefficients of variation were 5.1 and 2.9%, respectively. Concentrations of β-hydroxybutyrate (**BHB**; 137019910930, DiaSys Diagnostics, Holzheim, Germany), glucose (GN45126, RAL laboratories, Barcelona, Spain), calcium (GN12125, RAL laboratories, Barcelona, Spain), lactate dehydrogenase (**LDH**; GN42125, RAL laboratories, Barcelona, Spain), free fatty acids (**FFA**;

157819910935, DiaSys Diagnostics, Holzheim, Germany) and total proteins (**TP**; GN46125, RAL laboratories, Barcelona, Spain) were measured for blood serum using an automatic spectrophotometer (METROLAB 2300GL, RAL laboratories, Barcelona, Spain). The intra-assay coefficients of variation were 0.56, 2.10, 1.10, 1.92, 1.07, and 0.90% respectively. The inter-assay coefficients of variation were 2.15, 3.09, 2.16, 3.10, 1.15, and 1.43%, respectively. Further information regarding these laboratory techniques can be found in Supplementary Material S1.

Colostrum and milk chemical composition (fat, protein, lactose, and total solids) were determined using a MilkoScan™ Mars (FOSS IBERIA, Spain). Colostrum samples were diluted 1:4 (v/v) using deionized water based on the procedure described by Spina et al. (2021) and Soufleri et al. (2023). Colostrum and milk somatic cell count (**SCC**) were determined using a DeLaval cell counter (DeLaval, Tumba, Sweden). Samples with a SCC $\geq$ 3 000 10^3 cells/mL were diluted 1:5 (v/v) with saline solution as described by Kawai et al. (2013).

In addition, rectal temperature (**RT**) was measured at parturition before the IA (0 h) and at the milking parlour before each milking using a digital thermometer (Beurer, Germany).

Statistical analysis

The SAS POWER procedure (version 9.4, SAS Institute Inc., Cary, NC, USA) was used to determine the minimum number of animals needed in this study to identify significant differences at the 5% level with a power of 80%. Based on this, the minimum number of animals per group was ten (10). The main variable used in this procedure was IgG concentration in goat colostrum. According to Hernández-Castellano et al. (2016), the IgG concentration in *Majorera* goat colostrum is 41.1 mg/mL with a SD of 5.65 mg/mL, with a significant difference considered if IgG concentration differs > 5.7 mg/mL between groups.

Data were analysed using the MIXED PROCEDURE of SAS. The model included the IA (LPS vs. control), time (from parturition to d 30 postpartum) and the interaction between both (IA $\times$ Time) as fixed effects. The animal (i.e., goat) was considered as an individual subject and time as a repeated measure. The Tukey test was used to determine significant differences ($P < 0.05$) between groups. The homogeneity of the variance and the normality of the residuals were estimated graphically using PROC UNIVARIATE. Data for variables that did not meet these criteria were log-transformed ($\log_{10}$) to get a normal distribution of residues and homogeneity. Results are presented as Least Square Means ± SEM. Results that were log-transformed and then back-transformed are presented as Mean [Minimum and Maximum].

Results

In this study, the gestation length was 150 ± 2 days with an average litter size of 2.3 ± 0.56 kids. No clinical signs of mastitis (i.e., swollen, warmth, or pain in the udder) were observed in the LPS and control groups after the IA. No differences were observed in the individual DM intake among groups on either the fourth and fifth month before parturition (2.2 ± 0.21 and 2.2 ± 0.25 kg DM, respectively; $P > 0.05$) or the first month of lactation (2.2 ± 0.34 kg DM; $P > 0.05$). Similarly, no differences in BW were observed among groups on either the fourth and fifth month before parturition (68.8 ± 2.44 and 69.1 ± 2.23, respectively; $P = 0.390$) or the first month of lactation (67.9 ± 2.97$P = 0.489$).

Variables analysed in colostrum

Colostrum yield and chemical composition (i.e., lactose, protein, fat, and total solids) were not affected by the IA (Table 2; $P_{IA} \geq 0.065$) but were affected by time (Table 2; $P_{Time} \leq 0.002$). Colostrum yield increased from d 0.125 to d 2 (1.9 ± 0.22 and 2.4 ± 0.21 kg, respectively). In addition, lactose percentage increased from d 0.125 to d 2 (2.8 ± 0.14 and 3.8 ± 0.16%, respectively) whereas protein percentage decreased (10.2 ± 0.57 and 7.0 ± 0.62%, respectively). Fat and total solids increased from d 0.125 (8.8 ± 0.56 and 23.7 ± 1.0%, respectively) to d 0.5 (9.8 ± 0.64 and 30.0 ± 1.07%, respectively) decreasing afterwards until d 1 (5.6 ± 0.56 and 17.2 ± 0.94%, respectively) to increase again at d 2 (8.0 ± 0.64 and 26.1 ± 1.06%, respectively).

In contrast, SCC (Table 2; Fig. 1) was higher in the LPS group compared to the control group (3.5 ± 0.09 and 3.1 ± 0.09 $\log_{10}$ cells/mL, respectively; $P_{IA} = 0.011$). Similarly, both colostrum IgG concentration (Table 2; Fig. 2A) and IgG total mass (Table 2) were higher ($P_{IA} \leq 0.044$) in the LPS group (31.9 ± 4.80 mg/mL and 51.8 ± 6.22 g, respectively) compared to the control group (19.0 ± 4.80 mg/mL and 29.8 ± 6.23 g, respectively). In both groups, colostrum IgG concentration decreased from d 0.125 to d 2 relative to the IA (51.7 ± 4.74 mg/mL and 8.7 ± 4.86 mg/mL, respectively; $P_{Time} < 0.001$). Furthermore, IgM concentration (Table 2; Fig. 2B) and IgM total mass (Table 2) were also affected by the IA ($P_{IA} \leq 0.037$), with higher concentration in the LPS group (0.8 ± 0.08 mg/ml and 1.4 ± 0.23 g, respectively) than in the control group (0.5 ± 0.08 mg/mL and 0.8 ± 0.22 g, respectively). Colostrum IgM concentration also decreased from d 0.125 to d 2 relative to the IA (1.1 ± 0.08 mg/mL and 0.3 ± 0.08 mg/mL, respectively; $P_{Time} < 0.001$).

Variables analysed in milk

Milk yield was not affected by either the IA ($P_{IA} = 0.733$) or time ($P_{Time} = 0.513$). Protein, fat, and total solids percentages as well as IgG and IgM concentrations and total mass were not affected by the IA (Table 3; $P_{IA} \geq 0.309$). However, lactose percentage was affected by the IA as the LPS group showed lower values than control group (Table 3; 4.3 ± 0.08 and 4.6 ± 0.08%, respectively; $P_{IA} = 0.026$). Chemical composition was affected by time (Table 3; $P_{Time} < 0.001$). Protein, fat, and total solids percentages decreased from d 4 (5.2 ± 0.19, 5.3 ± 0.19, and 15.5 ± 0.29%, respectively) to d 30 (3.9 ± 0.19, 3.7 ± 0.19, and 13.2 ± 0.27%, respectively) while lactose percentage increased (4.2 ± 0.09 and 4.7 ± 0.09%, respectively). Milk SCC (Table 3; Fig. 1) was higher in the LPS group compared to the control group (2.9 ± 0.11 and 2.6 ± 0.11 $\log_{10}$ cells/mL, respectively; $P_{IA} = 0.004$). In both groups, SCC decreased from d 4 to d 30 (2.9 ± 0.11 and 2.6 ± 0.11 log10 cells/mL; $P_{Time} = 0.045$).

Rectal temperature and variables analysed in blood

A two-way interaction between the IA and time ($P_{IA \times Time} = 0.007$) was observed for RT (Table 4; Fig. 3). Rectal temperature increased in the LPS group from parturition (0 h) to d 0.125 relative to the IA (38.9 ± 0.16 °C and 39.6 ± 0.16 °C, respectively), decreasing afterwards until d 15 (38.4 ± 0.15 °C) and increasing again on d 30 relative to the IA (38.8 ± 0.15 °C). In the control group, RT decreased progressively after the IA to d 30 (38.9 ± 0.15 °C and 38.4 ± 0.15 °C, respectively).

No differences between groups were detected in plasma IgG and IgM concentrations (Table 4; $P_{IA} = 0.446$, $P_{IA} = 0.243$, respectively). However, IgG concentration in both groups increased from parturition to d 0.125 (5.7 [4.5–7.2] and 10.4 [8.2–13.2] mg/dL, respectively $P_{Time} < 0.001$) decreasing constantly until d 1 and then increasing until d 15 (4.5 [3.6–5.7] and 13.0 [10.5–16.2] mg/dL, respectively). In addition, IgM concentrations were also affected by time increasing from d 1 to d 15 (1.5 ± 0.12 and 2.0 ± 0.12 mg/mL, respectively; $P_{Time} < 0.001$) and then decreasing until d 30 (1.9 ± 0.12 mg/mL).

Table 2
Yield, chemical composition, and immunoglobulin concentrations in colostrum (d 0.125, 0.5, 1 and 2) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

	Groups		SEM	Fixed effects, *P*-value		
Variables	LPS	Control		IA	Time	IA × Time
Yield, kg	1.9	1.8	0.22	0.792	0.002	0.462
Lactose, %	3.2	3.5	0.15	0.111	0.002	0.204
Fat, %	7.5	8.6	0.42	0.065	<0.001	0.862
Protein, %	8.8	8.2	0.60	0.393	<0.001	0.641
Total solids, %	24.1	24.4	0.72	0.637	<0.001	0.378
SCC, log_{10} cells/mL	3.5	3.1	0.09	0.011	0.161	0.169
IgG, mg/mL	31.9	19.0	4.80	0.044	<0.001	0.515
IgG total mass, g	51.8	29.8	6.23	0.002	<0.001	0.644
IgM, mg/mL	0.8	0.5	0.08	0.037	<0.001	0.798
IgM total mass, g	1.4	0.8	0.23	0.010	<0.001	0.590

Abbreviations: LPS = group that received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5) diluted in 2 mL of saline solution 0.9% in each half udder; the control group received an IA with 2 mL of 0.9% saline solution in each half udder without LPS.; IA = intramammary administration; IA × Time = Interaction IA × Time; SCC = somatic cell count; IgG = Immunoglobulin G; IgM = Immunoglobulin M.

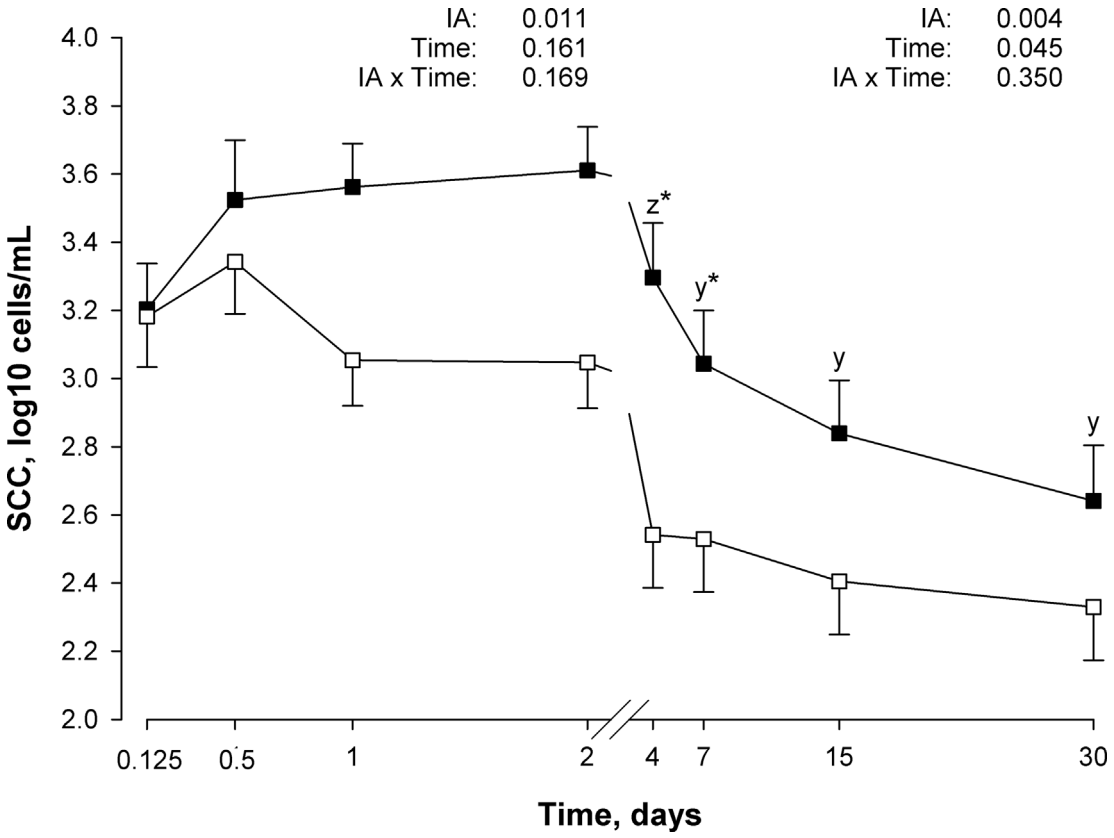

Fig. 1. Somatic cell count (SCC) in colostrum (d 0.125, 0.5, 1 and 2 relative to the IA) and milk (d 4, 7, 15 and 30 relative to the IA) throughout the experimental period in goats from the LPS (■) and control (□) groups. Different letters (z-y) indicate significant differences ($P < 0.05$) in milk in the LPS group. Significant differences between both groups are represented with (*). Abbreviations: IA = Intramammary administration. Data are expressed as least square means ± SEM.

Serum BHB, Glucose, Calcium, LDH, FFA and TP were not affected by the IA (Table 4; $P_{IA} \geq 0.087$) but were affected by time ($P_{Time} \leq 0.004$). Serum BHB concentrations decreased progressively from parturition to the end of the experimental period (1.2 [0.9–1.6] mmol/L and 0.6 [0.4–0.8] mmol/L, respectively). Glucose concentrations decreased from parturition to d 2 (90.1 [80.0–101.4] mg/dL and 37.8 [33.6–42.6] mg/dL, respectively) and then increased constantly until d 30 (49.6 [44.5–55.3] mg/dL). Similarly, calcium concentrations decreased from parturition to d 2 (8.5 ± 0. 24 mg/dL and 8.0 ± 0.24 mg/dL, respectively) and increased progressively until the end of the experimental period (9.4 ± 0.24 m g/dL). Serum LDH activity increased constantly from parturition to d 15 (427.4 ± 28.58 U/L and 515.0 ± 28.58 U/L, respectively) showing a decrease on d 30 (510.3 ± 28.58 U/L). Serum FFA concentrations decreased progressively from parturition to the end of the experimental period (1.4 ± 0.08 mmol/L and 0.5 ± 0.08 mmol/L, respectively). Total protein concentrations decreased from parturition to d 1 (6.3 ± 0.18 g/dL and 5.9 ± 0.18 g/dL, respectively) and then increased constantly until d 30 (7.1 ± 0.18 g/dL).

Discussion

The IA of LPS to mimic a mastitis caused by Gram-negative bacteria has been used in dairy species since the 1980s. Some of these studies assessed the effect of LPS administration on mammary

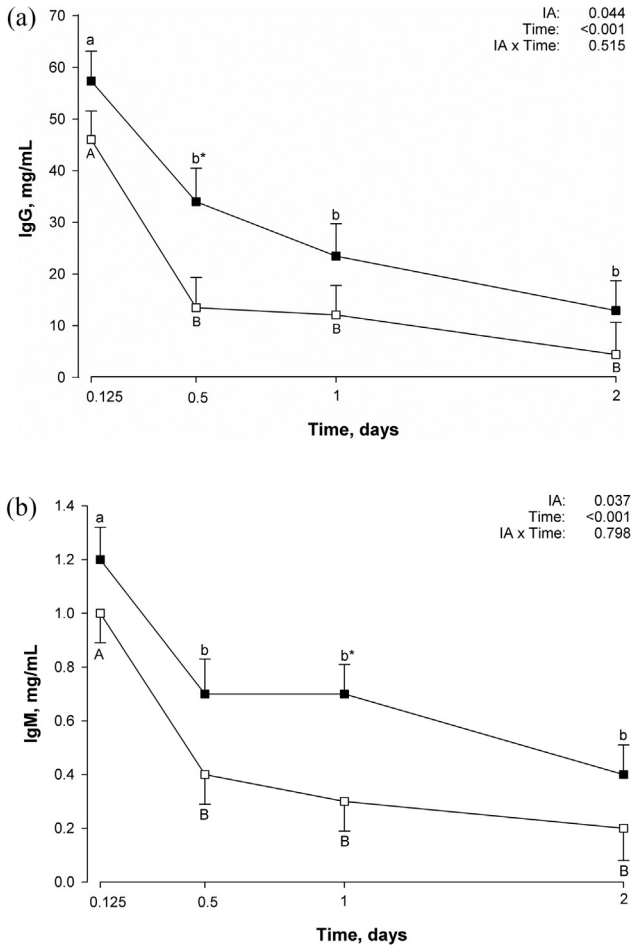

Fig. 2. Immunoglobulin G (A, IgG) and immunoglobulin M (B, IgM) in colostrum (d 0.125, 0.5, 1 and 2 relative to the IA) of goats from the LPS (■) and control (□) groups. Different letters (a-b) indicate significant differences ($P < 0.05$) in the LPS group. Different letters (A-B) indicate significant differences ($P < 0.05$) in the control group. Significant differences between both groups are represented with (*). Abbreviations: IA = Intramammary administration. Data are expressed as least square means ± SEM.

blood flow (Dhondt et al., 1977), mastitis development (Johnzon et al., 2018), systemic responses (Sintes et al., 2020), drug efficacy (Wall et al., 2016b), and milk composition (Wellnitz and Bruckmaier, 2021). However, the use of an IA of LPS to intentionally enhance dairy goat colostrum and milk composition has never been tested.

In the present study, the IA of LPS did not affect colostrum yield or chemical composition but enhanced IgG and IgM concentrations compared to the animals that received the IA of saline without LPS. In dairy cows, the IA of LPS can modify the blood-milk barrier permeability, enhancing the transfer of immune components, in particular IgG, within the first 3 h after the IA (Wellnitz et al., 2013; Lehmann et al., 2013). In this study, 50 μg of LPS were applied to dairy goats immediately after parturition, 3 h before first milking. Previous studies have demonstrated that the milk ejection reflex and the associated oxytocin release occurs in response to suckling or milking (Hernandez et al., 2002; Belo and Bruckmaier, 2010). Therefore, to avoid triggering the onset of lactogenesis and subsequent changes in colostrum composition, no samples were collected before the first milking at 3 h. Both the dose of LPS and the timing of administration used in the present study could explain the results obtained. Higher doses of intramammary LPS (i.e., 100 μg) in empty udders can cause greater and faster tissue damage, promoting immune responses and composition changes shortly after administration (Werner-Misof et al., 2007b). In this study, the IA of LPS was performed immediately after parturition, and therefore, in full udders. The presence of colostrum in the udder may reduce the interaction between LPS molecules and the mammary tissue, causing a delayed immune response which could explain the different effects observed in previous studies. Despite the permeability of the blood-milk barrier was not determined in the present study, it is likely that the increased concentration of immunoglobulins (i.e., IgG and IgM) in colostrum might be caused by leakage of components from blood to the mammary gland during inflammation. In mice, the IA of LPS can induce changes in claudins which are essential transmembrane proteins to maintain blood-milk barrier permeability (Kobayashi et al., 2013). Colostrum immunoglobulins can be either synthesized in the mammary gland or transferred from the bloodstream during colostrogenesis (Hernández-Castellano et al., 2018). Although IgG subclasses (i.e., IgG_1 and IgG_2) have been widely described in bovine colostrum (Barrington et al., 1997; Stelwagen et al., 2009), they have not been fully investigated in goats as no specific antibodies are available for this determination. Wall et al. (2015) described that these subclasses are transferred to colostrum and milk by different mechanisms during mastitis, showing that IgG_1 is actively transported by FcRn receptors whereas IgG_2 is more likely to diffuse passively through the blood-milk barrier. Furthermore, inflammatory agents such as cytokines can induce an over-expression of FcRn receptors promoting greater IgG_1 transfer to the mammary gland (Jiang et al., 2016). These findings suggest a potential effect of the IA of LPS on the mammary gland immune response and, therefore, could be used to intentionally modulate the permeability of the blood-milk barrier to increase colostrum and milk immune components in dairy species.

Besides the effect of the IA of LPS on colostrum immunoglobulin concentrations, an increased SCC in colostrum and milk was also observed. Several studies have demonstrated that the intensity of the immune response is dose-related (Van Oostveldt et al., 2002), being more intense at high doses as the greater damage to the tight junctions causes increased flow of inflammatory cells into milk (Baumert et al., 2009). In fact, Werner-Misof et al., (2007a) reported that SCC in bovine mammary glands treated with different LPS doses (i.e., 6.25, 12.5, 25, 50, and 100 μg in 10 mL of saline) reaches the maximum value within the first 12 h post-treatment according to the applied dose. Baumert et al. (2009) also detected an increased SCC in dairy cows at 10 h after the IA, but these differences were no longer observed after 24 h. In contrast, the present study demonstrates that the effect of IA on LPS seems to be extended in dairy goats, even after the LPS molecule has been removed, as differences among groups were still present 48 h after the IA. Similarly, Salama et al. (2020) observed increased SCC in dairy goats 72 h after the IA. Differences of SCC among studies might be explained by the dose, timing of LPS administration and the species used in the study. Low doses of intramammary LPS in dairy cows did not induce clinical signs of inflammation or SCC increase (Werner-Misof et al., 2007b). In addition, high doses of LPS applied in full udders might result in lower or delayed responses to inflammation than in empty udders, which are directly exposed to LPS. Intramammary administration of LPS before or after milking can determine different timing in the inflammation process and consequently can modulate the immune cell migration to the udder.

Although no changes were observed in colostrum chemical composition, the IA of LPS caused reduced lactose percentage in milk. This change in chemical composition could be caused by tissue damage and modifications on the blood-milk barrier permeability during inflammation, affecting the synthesis and transfer

Table 3
Yield, chemical composition, and immunoglobulin concentrations in milk (d 4, 7, 15 and 30) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

	Groups		SEM	Fixed effects, *P*-value		
Variables	LPS	Control		IA	Time	IA × Time
Yield, kg	2.5	2.4	0.18	0.733	0.513	0.842
Lactose, %	4.3	4.6	0.08	0.026	<0.001	0.927
Fat, %	4.3	4.5	0.15	0.309	<0.001	0.065
Protein, %	4.4	4.3	0.16	0.676	<0.001	0.161
Total solids, %	14.1	14.4	0.22	0.450	<0.001	0.602
SCC, log_{10} cells/mL	2.9	2.5	0.11	0.004	0.045	0.350
IgG, mg/mL	0.8	0.9	0.10	0.468	0.035	0.159
IgG total mass, g	1.9	2.0	0.17	0.899	0.004	0.111
IgM[1], μg/mL	105.0 [90.2–122.2]	96.3 [82.8–112.1]	–	0.458	<0.001	0.258
IgM total mass, g	0.3	0.2	0.03	0.310	<0.001	0.304

Abbreviations: LPS = group that received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5) diluted in 2 mL of saline solution 0.9% in each half udder; the control group received an IA with 2 mL of 0.9% saline solution in each half udder without LPS; IA = intramammary administration; IA × Time = Interaction IA × Time; SCC = somatic cell count; IgG = Immunoglobulin G; IgM = Immunoglobulin M.
[1] Mean, minimum and maximum obtained from the log10 transformation.

Table 4
Concentrations of plasma immunoglobulins (IgG and IgM) and serum metabolites, as well as rectal temperature (d 0.125, 0.5, 1, 2, 4, 7, 15 and 30) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

	Groups		SEM	Fixed effects, *P*-value		
Variables	LPS	Control		IA	Time	IA × Time
IgG,[1] mg/mL	8.4 [7.2–9.7]	7.7 [6.7–9.0]	–	0.446	<0.001	0.744
IgM, mg/mL	1.6	1.8	0.11	0.243	<0.001	0.775
BHB,[1] mmol/L	0.8 [0.6–1.1]	1.0 [0.7–1.3]	–	0.611	0.002	0.729
Glucose,[1] mg/dL	48.2 [40.2–54.3]	48.4 [45.3–51.8]	–	0.883	<0.001	0.430
Calcium, mg/dL	8.6	8.5	0.13	0.347	<0.001	0.699
LDH, U/L	490.1	456.6	23.1	0.313	0.004	0.302
FFA, mmol/L	0.9	0.9	0.05	0.782	<0.001	0.667
TP, g/dL	6.5	6.2	0.14	0.087	<0.001	0.976
RT, °C	39.0	38.7	0.07	0.002	<0.001	0.007

Abbreviations: LPS = group that received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5) diluted in 2 mL of saline solution 0.9% in each half udder; the control group received an IA with 2 mL of 0.9% saline solution in each half udder without LPS; IA = intramammary administration; IA × Time = Interaction IA × Time; IgG = Immunoglobulin G; IgM = Immunoglobulin M; BHB = β-hydroxybutyrate; LDH = lactate dehydrogenase; FFA = free fatty acids; TP = total protein; RT = rectal temperature.
[1] Mean, minimum and maximum, obtained from log10 transformation.

of components. Reduced lactose percentages in milk during mastitis have been associated with increased SCC (Antanaitis et al., 2021), increased transfer of lactose to the bloodstream (Chedly et al., 2010), and the use of lactose by pathogens as a source of energy (Silanikove et al., 2014). Changes in lactose percentages can be also associated with negative energy balance after parturition (Ptak et al., 2012; dos Santos et al., 2019). Similarly, Salama et al. (2020) did not observe differences in milk yield between LPS-treated and untreated mammary glands but found greater milk protein content and lower lactose percentages in LPS-challenged udder-halves of *Murciano-Granadina* goats. In addition, other authors observed lower milk yields during the first 24 h after the LPS challenge in dairy ewes and cows (Castro-Costa et al., 2014; Shangraw et al., 2020), as well as lower lactose content, supporting that induced mastitis can affect milk composition. The milk secretion mechanism in dairy goats (i.e., apocrine secretion) compared to cows and ewes (i.e., merocrine secretion) could explain the different effects of LPS on milk yield in these species (Paape and Capuco, 1997; Souza et al., 2012). During mastitis, casein degradation causes the release of active peptides that down-regulate milk secretion in cows, ewes and goats (Silanikove et al., 2000; Leitner et al., 2008). However, the greater content of casein and plasmin activity in cow and ewe milk compared to goat milk could also explain the lack of variation in goat milk yield after the IA of LPS.

Despite the changes observed in colostrum and milk composition, as well as the increased RT caused by the IA, no differences in plasma IgG and IgM concentrations were observed during the entire experimental period. These findings are in agreement with the results described by Lehmann et al. (2013), who found no variation on serum IgG concentration in cows that received an IA of LPS. These findings would indicate a short-term systemic response to the locally induced infection which was not sufficient to increase IgG and IgM concentrations on the bloodstream. Similarly, Salama et al. (2020) and Gross et al. (2020) observed an increase of RT in LPS-challenged dairy goats (i.e., within the first 8 h after the IA) and Holstein cows (i.e., within the first 5 h after the IA), respectively.

Although the present study shows no changes in blood serum metabolites associated to the IA of LPS, some variations were detected throughout the experimental period. Thus, serum BHB was elevated at parturition and decreased progressively until d 30 relative to the IA. According to Baird and Pugh (2002), blood concentrations of BHB above 0.8 mmol/L are indicative of negative energy balance in ewes, so these results might be explained by the high energy demand at the onset of lactation. For the same reason, glucose and FFA were also elevated immediately after parturition.

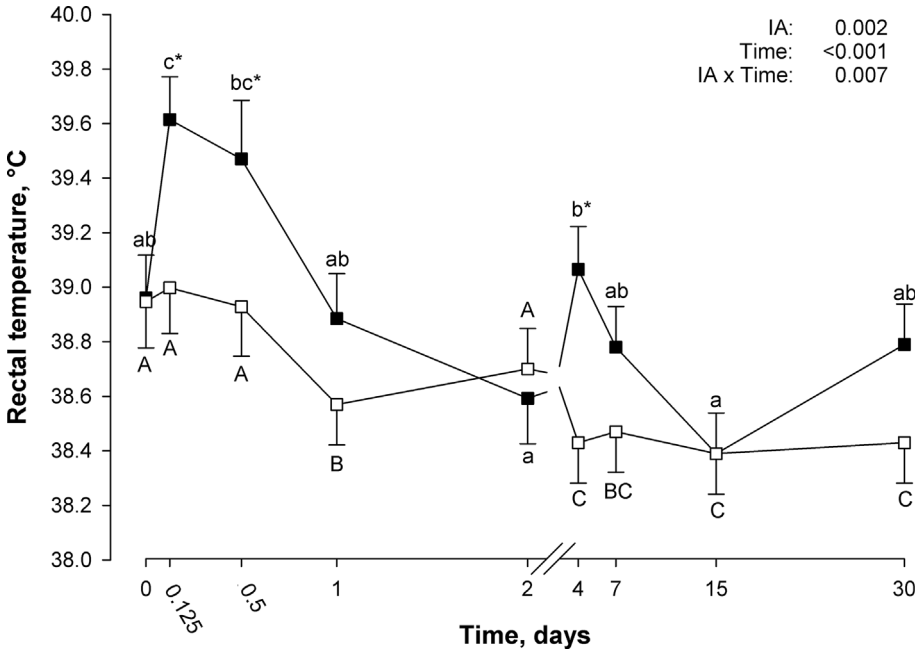

Fig. 3. Rectal temperature throughout the experimental period in goats from the LPS (■) and control (□) groups. Different letters (a–c) indicate significant differences ($P < 0.05$) over time in the LPS group. Different letters (A–C) indicate significant differences ($P < 0.05$) over time in the control group. Significant differences between both groups are represented with (*). Abbreviations: IA = Intramammary administration. Data are expressed as least square means ± SEM.

Conclusion

The intramammary administration of lipopolysaccharides in dairy goats at parturition can modify colostrum composition, increasing immunoglobulin concentrations (i.e., IgG and IgM) and somatic cell count. These results might be associated with the increased blood-milk barrier permeability and immune response caused by the intramammary administration of lipopolysaccharides. This study could set the baseline for future studies on the modulation of the blood-milk barrier at parturition to enrich goat colostrum quality under experimental conditions. However, further studies must be conducted to determine the suitability of LPS as a tool to increase colostrum quality in practical conditions such as dairy farms.

Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.animal.2024.101082.

Ethics approval

The experiment was approved by the Ethical Committee for Animal Experimentation of the Universidad de Las Palmas de Gran Canaria following the national legislation (OEBA-ULPGC; Procedure 27/2021).

Data and model availability statement

None of the data were deposited in an official repository. The data presented in this study are available on request from the corresponding author.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use any artificial intelligence-assisted technologies in the writing process.

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Declaration of interest

None.

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