Effects of colostrum instead of formula feeding for the first 2 days postnatum on whole-body energy metabolism and its endocrine control in neonatal calves

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ABSTRACT

Colostrum provides high amounts of nutritive and non-nutritive substrates, which are essential for calf nutrition and passive immunization. Colostral growth factors and hormones have beneficial effects on postnatal maturation and may affect substrate utilization and energy expenditure in neonatal calves. We tested the hypothesis that energy metabolism and its endocrine regulation differ during the first 10 d of life in calves fed either colostrum or a milk-based formula with a similar nutrient composition to colostrum, but largely depleted of bioactive substances, for the first 2 d postnatum. Male Holstein calves (n = 18) were fed either pooled colostrum (COL; n = 9) or a milk-based formula (FOR; n = 9) for the first 2 d of life. From d 3 on, all calves received same milk replacer. On d 2 and 7 of life, calves were placed in a respiration chamber for indirect calorimetric measurements to calculate heat production, fat (FOX) and carbohydrate oxidation (COX), as well as respiratory quotient. Blood was sampled on d 1 before first colostrum intake and on d 2, 3, 7, 8, 9, and 10 before morning feeding, to measure plasma concentrations of immunoglobulins, metabolites, and hormones. Additional postprandial blood samples were taken on d 1 and 9 at 30, 60, 120, 240, and 420 min after milk feeding. Liver samples were collected on d 10 of life to determine gene expression related to energy metabolism. Formula-fed calves showed lower plasma concentrations of total protein, immunoglobulins, haptoglobin, leptin, adiponectin, and insulin-like growth factor (IGF) binding protein (IGFBP)-4 during the whole study but temporarily higher plasma concentrations of urea, insulin, glucagon, triglyceride, and cholesterol on the first day after feeding, compared with concentrations in COL. The temporary increase in glucagon, triglyceride, and cholesterol on d 1 reversed on d 2 or 3, showing higher concentrations in COL than in FOR calves. In FOR, IGF-I, IGFBP-2, and IGFBP-3 were lower on d 3 than in COL. Interestingly, FOR calves had higher heat production during respiratory measurements on d 2 and higher body temperature on d 2, 3, and 5 than those of COL. The hepatic mRNA abundance of cytosolic phosphoenolpyruvate carboxykinase was higher in FOR than in COL. Our results indicate that first milk feeding after birth influenced whole-body energy expenditure but not FOX and COX in neonatal calves, and the absorption of colostral leptin and adiponectin might affect insulin sensitivity on d 1 of life.

Key words: calf, colostrum, energy metabolism, energy expenditure, biologically active substances

INTRODUCTION

Newborn calves rely on colostrum intake immediately after birth for nutrient supply and for establishing passive immunity (Quigley and Drewry, 1998; Barrington and Parish, 2001). In addition to its high content of nutrients and immunoglobulins, bovine colostrum contains high amounts of non-nutritive, biologically active substances, such as hormones and growth factors (Blum and Hammon, 2000; Blum and Baumrucker, 2008; Nissen et al., 2017), which may have local and systemic effects on postnatal maturation in neonatal calves (Blum, 2006; Hammon et al., 2012; Ontsouka et al., 2016). Colostrum intake immediately after birth

has a great effect on the intestinal development of the neonatal calf and supports nutrient absorption by the intestine (Roffler et al., 2003; Blum, 2006; Hammon et al., 2012). Glucose supply is clearly improved in colostrum-fed calves compared with calves fed a formula with the same lactose content as colostrum but much lower amounts of biologically active factors (Steinhoff-Wagner et al., 2011; Gruse et al., 2015). Colostrum intake affects the neonatal metabolome, indicating large systemic effects on neonatal metabolism after first colostrum intake (Hammon et al., 2012; Qi et al., 2018; Zhao et al., 2018). Furthermore, thermoregulatory mechanisms, including the metabolism of brown adipose tissue, shivering, and physical activity, are important for adaptation to new environmental conditions after birth, and colostrum intake stimulates heat production in neonatal calves (Vermorel et al., 1983). However, less is known about the effects of first colostrum feeding on whole-body nutrient utilization during the first week of life in neonatal calves and whether long-lasting effects on carbohydrate (**COX**) and fat oxidation (**FOX**) occur due to colostrum feeding.

Neonatal energy metabolism is under endocrine control (Blum and Hammon, 2000; Blum, 2006; Hammon et al., 2012), but the importance of colostral hormones and growth factors for metabolic regulation of the neonate are still not clear. Previous studies indicate that the interaction of numerous growth-enhancing factors in the first colostrum stimulates intestinal maturation and protein synthesis in several tissues of the neonate (Reeds et al., 2000; Roffler et al., 2003). On the other hand, the systemic effects of colostral IGF-I or insulin were denied because studies could not detect a significant intestinal absorption of colostral IGF-I or insulin in neonatal calves (Grütter and Blum, 1991; Vacher et al., 1995; Sparks et al., 2003) or piglets (Donovan et al., 1997). However, recent studies in neonatal calves indicated systemic availability of colostral adiponectin (Kesser et al., 2015). The effect of colostral adiponectin on metabolic development in neonatal calves is not yet clear, but adiponectin may influence neonatal energy metabolism by affecting insulin action (Havel, 2002; Yamauchi and Kadowaki, 2013). In addition, lactocrine maternal programming of neonatal reproductive tract development has been discussed in piglets (Bagnell and Bartol, 2019).

The present study aimed to investigate the differences in energy metabolism between colostrum- and formula-fed calves, using respiratory measurements combined with metabolic and endocrine studies in blood plasma and liver. We tested the hypothesis that calves fed a milk-based formula without growth-promoting substances for the first 2 d of life might suffer from impaired neonatal energy metabolism, indicated by changes in COX and FOX and by insufficient endocrine regulation of postnatal energy metabolism during the first 10 d of life.

MATERIALS AND METHODS

The present study was conducted at the experimental station of the Leibniz Institute for Farm Animal Biology (FBN). The experimental housing conditions of the calves and the experimental procedures were in accordance with the guidelines of the German Animal Protection Law and were approved by the Landesamt für Landwirtschaft, Lebensmittelsicherheit und Fischerei Mecklenburg-Vorpommern (LALLF M-V), Rostock (registration number: 7221.3–1-010/14).

Animals, Experimental Design, and Husbandry

A total of 18 male calves (Holstein Friesian) from pluriparous cows from the herd of the local State Farm (Gut Dummerstorf GmbH, Dummerstorf, Germany) were used to investigate the effects of colostrum or formula feeding on energy metabolism during the neonatal period.

The parturitions were monitored, and calves were separated immediately from their dams and randomly allocated to the feeding groups. Calves had no access to colostrum of their dams after birth. During the first 2 d of life, calves in the colostrum group (**COL**; n = 9) received pooled frozen colostrum from milkings 1 (d 1 of life) and 3 (d 2 of life) after parturition. Calves in the formula group (**FOR**; n = 9) received frozen milk-based formula (Bergophor Futtermittelfabrik; Dr. Berger GmbH and Co, Kulmbach, Germany) for d 1 and 2, with a macronutrient composition that was comparable to the corresponding colostrum milkings (Table 1) but that contained only trace amounts of bioactive factors (Rauprich et al., 2000; Hammon et al., 2003; Steinhoff-Wagner et al., 2011). On the first day of life, colostrum or formula were fed at 10% of BW to each calf and on d 2 at 12% of BW. From d 3 after birth onward, all calves were fed milk replacer (**MR**) at an amount of 12% of BW (150 g powder/L water; Salvalac Mirapro 45; Salvana Tiernahrung, Klein-Offenseth Sparrieshoop, Germany; Table 1), which was provided in 2 meals per day. Two calves of the FOR group became sick: one calf developed aspiration pneumonia on the second day of life, and the other a purulent pneumonia on the seventh day of life. These calves were excluded from the study and were replaced by 2 other male calves from the herd.

Calves were held in individual boxes (1.4 m × 2.45 m) on straw in a room at the animal husbandry facility

of the Leibniz Institute, with automated air conditioning providing a constant temperature of 20°C and 50% relative humidity. All calves were born during night or in the morning (from 0200 h up to 1200 h). Calves received their first colostrum or formula within 2 h after birth through a nipple attached to a bottle. Second feeding was 10 h later. From d 2 of age, colostrum or formula and MR were fed at 0700 h and 1700 h. During the first 2 d of life, refused liquid feed was tube-fed to attain the desired feed intake. The study lasted either 10 (11 calves: 6 COL and 5 FOR) or 11 d (7 calves; 3 COL and 4 FOR). In 11-d cases, calves were fed 1 additional day with MR before conducting final investigations. Mean age in COL calves was (mean ± SE) 9.52 ± 0.17 d; mean age in FOR calves was 9.31 ± 0.17 d. During the entire trial, animals had free access to chopped hay and water. Navels were disinfected with 10% povidone iodine solution (Vet-Sept; aniMedica, Senden-Bösensell, Germany). Calves received an oral dose of 1 g of iron dextran with their first meal on d 1 (Ursoferran; Serumwerk Bernburg, Bernburg, Germany). To support immunological defense during the first 5 d of life in formula-fed calves but avoid differences in medical care between groups, all calves received chicken egg-derived immunoglobulins with the morning feeding (0.25 g/kg of BW; Globigen Life Start 25%, EW Nutrition, Visbek, Germany). To prevent cryptosporidiosis, calves were treated orally with halofuginone (0.1 mg/kg of BW; Halocur, Intervet, Igoville, France) after the evening feeding from d 1 to 7. All calves received subcutaneous injections of B-vitamins (100 mg nicotinamide/calf, 40 mg thiamin chloride hydrochloride/calf; Vitamin-B-Komplex, Serumwerk Bernburg, Germany). In addition, formula-fed calves received bovine colostral immunoglobulins with antibodies against *Escherichia coli*, rotavirus, and coronavirus (2 g immunoglobulins/d; Aniserin orinject, aniMedica, Seden-Börsensell, Germany) via subcutaneous injection on d 1 and orally on d 3 and 5, as recommended by the manufacturer. Furthermore, formula-fed calves were treated prophylactically with colistin sulfate from d 2 to 8 (3 mg/kg of BW, i.m.; Belacol, BelaPharm, Vechta, Germany).

Data Collection and Sampling Procedure

Body weights were recorded at 1, 2, 3, 7, 8, 9, and 10 d of age. Body temperature was measured twice daily before feeding. Blood samples were collected from the jugular vein at 1, 2, 3, 7, 8, 9, and 10 d of life. After shaving and disinfecting the skin, the vein was punctured, and blood at 2, 3, 7, 8, and 10 d of age was collected before morning feeding in evacuated tubes (Greiner Bio-One GmbH, Frickenhausen, Germany) containing sodium fluoride (2 to 4 mg/mL) and potassium oxalate (1 to 3 mg/mL) for measurements of metabolites and potassium-EDTA (1.8 mg/mL) for hormone measurements. Blood samples were held on ice until centrifugation at $1.565 \times g$ for 20 min at 4°C. The supernatants from plasma were pipetted into aliquots and stored at −20°C until further analysis. Immediately after birth and on d 9 of life, blood samples were taken before and at 30, 60, 120, 240, and 420 min after the morning feeding via catheter (Cavafix Certo with Splittocan, B. Braun Melsungen AG, Melsungen, Germany), which were placed into the jugular vein. After shaving and disinfecting the skin, a needle (1.8 × 2.4 mm; 14G) was inserted into the vein, and afterward the needle was replaced by the catheter (tube with 1.1 × 1.7 mm; 16G).

Two hours after morning feeding on d 10 or 11 of life, approximately 300 mg of liver tissue was collected from each calf by biopsy with the use of a custom-made biopsy trocar (400 mm length; Gruse et al., 2015). Liver samples were frozen in liquid nitrogen and stored at −80°C.

Milk Analyses

The chemical composition of colostrum and formula pools was analyzed by Qualitätsprüfungs- und Dienstleistungsgesellschaft Mecklenburg-Vorpommern

Table 1. Chemical compositions of colostrum milkings, formulas, and milk replacer[1]

Item	Colostrum, d 1	Colostrum, d 2	Formula 1, d 1	Formula 2, d 2	Milk replacer
DM, g/kg	217.9	142.3	197.0	153.0	150.0
CP, g/kg of DM	608.4	481.6	545.0	400.0	202.0
Ether extract, g/kg of DM	171.0	247.0	170.0	250.0	191.0
Lactose, g/kg of DM	94.1	140.3	179.0	236.0	515.0
Crude ash, g/kg of DM	Not determined	Not determined	55.0	65.0	73.5

[1]The compositions of formulas 1 and 2 (Bergophor Futtermittelfabrik, Dr. Berger GmbH and Co., Kulmbach, Germany) were as follows (per kg of DM): whey powder (173.3 g and 277.8 g, respectively), lactalbumin powder (495.0 g, 180.0 g), casein powder (138.6 g, 257.2 g), plant oil (coconut and palm; 163.4 g, 254.1 g), premix (29.7 g, 30.9 g), plus 10 g mono-calcium-phosphate, 10 g calcium carbonate, 1 g sodium chloride, 50,000 IU vitamin A, 30 mg α-tocopherol acetate, 20 mg iron, 1.0 mg β-carotene, 0.15 mg copper, and 20 mg selenium. Milk replacer (per g of DM; Salvalac Mirapro 45, Salvana Tiernahrung, Klein-Offenseth Sparrieshoop, Germany): whey powder (350.0 kg), skim milk powder (450.0 g), plant oil (coconut, palm, soybean; 180.0 g); premix (20.0 g; Salvana Tiernahrung): 50,000 IU vitamin A, 4,000 IU vitamin D_3, 200 mg α-tocopherol acetate, 120 mg iron, 48 mg zinc, 46 mg manganese, 9.0 mg copper, 0.18 mg cobalt, 0.5 mg iodine, and 0.4 mg selenium (Gruse et al., 2015).

(MQD, Güstrow, Germany). Dry matter, CP, crude fat, lactose, and ash were determined according to Weender standard procedures (Naumann and Bassler, 2006). The MR used in this study was the same as reported in a previous study (Gruse et al., 2015).

Blood Analyses

Plasma concentrations of albumin, total protein, glucose, lactate, cholesterol, triglycerides, nonesterified fatty acids (**NEFA**), and urea were determined using an automatic spectrophotometer (ABX Pentra 400; Horiba ABX SAS, Montpellier, France) with kits from Horiba ABX (lactate: A11A01721; albumin: A11A01664; triglycerides: A11A01640), MTI Diagnostics (Idstein, Germany; glucose: 5530230; total protein: 553–412; cholesterol: 553–127), Labor + Technik E. Lehmann (Berlin, Germany; urea: LT UR0010), and WAKO Chemicals (Neuss, Germany; NEFA: 43691995). Intra-assay coefficients of variation were below 0.1% for all parameters.

Plasma concentrations of IgG1, IgG2, and IgM (all Ig were not measured postprandially on d 9) were determined via ELISA (no. E10–116, E10–101, E10–117, Bethyl Laboratories Inc., Montgomery, TX; Gruse et al., 2016). The intra- and interassay coefficients of variation were 3.1% and 2.7% for IgG1, 2.8% and 1.7% for IgG2, and 4.2% and 2.9% for IgM. Plasma concentrations of haptoglobin were measured in duplicate by ELISA (Hiss et al., 2004). Intra- and interassay coefficients of variation for haptoglobin were 3.9% and 12.2%, respectively. Plasma concentrations of insulin (#RIA-1257) and glucagon (#RIA-1258) were determined by RIA, using kits from DRG Instruments GmbH (Marburg, Germany), which were adapted to bovine subjects (Hammon et al., 2009). The intra- and interassay coefficients of variation were 3.7% and 5.5% for insulin and 3.4% and 20.0% for glucagon. The plasma cortisol concentration was analyzed in duplicate after extraction with diethylether, using a commercially available ELISA kit (#EIA1887; DRG Instruments; Gruse et al., 2016). Intra- and interassay coefficients of variation were 5.3% and 12.1%, respectively. Plasma IGF-I, growth hormone (**GH**), and total (free and carrier-bound) 3,5,3′-triiodothyronine (T_3) and thyroxine (T_4) concentrations were measured by RIA in triplicate (Vicari et al., 2008). Intra- and interassay coefficients of variation for all RIA were below 10% and 15%, respectively. Levels of IGF-binding proteins (**IGFBP**-2, -3, and -4) were determined only in basal plasma samples, via western ligand blot analysis (Laeger et al., 2014; Frieten et al., 2018). Interassay variation was 14% for IGFBP-3 and 7.5% for IGFBP-2. Plasma leptin and adiponectin concentrations were determined via enzyme immunoassay in duplicate, and intra- and interassay coefficients of variation were 6.3% and 13.9% for leptin and 7.0% and 11.0% for adiponectin (Sauerwein et al., 2004; Mielenz et al., 2013), and HPLC was used to examine plasma adrenaline and noradrenaline concentration in duplicate (Weber et al., 2013). The intra- and interassay coefficients of variation were 4.5% and 9.4% for adrenaline and 1.8% and 3.0% for noradrenaline.

Glycogen Concentration and Gene Expression Related to Energy Metabolism in the Liver

Glycogen concentration was determined through use of a commercial kit based on amyloglucosidase-catalyzed glucose release (no. 10207748035; Roche Diagnostics GmbH, Mannheim, Germany). The isolation of RNA from liver samples was previously described by Schäff et al. (2016). Briefly, the frozen tissue was transferred to a mortar containing liquid nitrogen and ground with a pestle to a fine powder. For extraction, 50 to 60 mg of the sample material was covered with TRIzol Reagent (Life Technologies, Darmstadt, Germany) and homogenized using a cell disrupter system (FastPrep FP120A-230; Thermo Electron Corporation, Milford, MA). For digestion of contaminating genomic DNA and purification of the samples, RNASE-Free DNase (Qiagen GmbH, Hilden, Germany) and RNeasy Mini Kit (Qiagen) were used.

The integrity and quality of total RNA were confirmed via gel electrophoresis and by measuring the RNA integrity number (RIN) value with a bioanalyzer using the Agilent RNA 6000 Nano Kit (Agilent Bioanalyzer 2100, Hamburg, Germany). The mean RIN for liver tissue was, on average, 6.8. The quantity and quality of the total RNA was also measured by optical density via a spectrophotometer (NanoPhotometer, Implen GmbH, Munich, Germany) at 260:280, of which the ratio ranged from 1.8 to 2.0.

For cDNA synthesis, 750 µg of RNA was reverse-transcribed with 200 U of Reverse Transcriptase MMLV-RT RNase (H−) Point Mutant (Promega, Madison, WI) and 250 pmol random hexamer primer (Metabion International AG, Planegg-Steinkirchen, Germany). The cDNA was diluted 1:4 with diethyl pyrocarbonate (DEPC) water, and aliquots were stored at −80°C.

Specific primers were used to measure the mRNA expression of glycogen phosphorylase (*PYGL*), glucose-6-phosphatase (*G6PC*), phosphoenolpyruvate carboxykinase (cytosolic: *PCK1*; mitochondrial: *PCK2*), pyruvate carboxylase (*PC*), propionyl-CoA carboxylase α (*PCCA*), carnitine-palmitoyl-transferase 1A (*CPT1A*), acyl-CoA dehydrogenase very long chain (*ACADVL*), apolipoprotein A1 (*APOA1*), 3-hydroxyl-3-methyl-glutaryl-CoA synthase 1 and 2 (*HMGCS1*,

HMGCS2), sterol regulatory element binding factor 1 (*SREBF1*), peroxisome proliferator-activated receptor (*PPARG*), growth hormone receptor (*GHR*) and the liver-specific variant (*GHR1A*), IGF-I (*IGF1*), IGFBP-2 (*IGFPB2*), and IGFBP-3 (*IGFBP3*), insulin receptor (*INSR*), α_1-adrenergic receptor (*ADRA1B*), β2-adrenergic receptor (*ADRB2*), and glucocorticoid receptor (*NR3C1*). Specific primer pairs were designed using Primer-BLAST (https://www.ncbi.nlm.nih.gov/tools/primer-blast/) or according to previous studies, as listed in Supplemental Table S1 (https://doi.org/10.3168/jds.2019-17708).

The quantitative real-time PCR was conducted in duplicate on a LightCycler 2.0 (Roche) using 2 µL of cDNA and a Luminaris Color HiGreen qPCR Master Mix (Thermo Fisher Scientific Inc., Waltham, MA). After an initial denaturation step at 95°C for 15 s, 40 cycles of annealing for 15 s and elongation at 72°C for 30 s followed. After the last amplification cycle, a melting curve analysis was performed to generate single PCR products. Agarose gel electrophoresis followed, to confirm product purity and size. Subsequent sequencing was performed using an ABI 3130 Genetic Analyzer (Life Technologies). The efficiency was calculated using LinRegPCR 2013 software (Ruijter et al., 2009). Samples with an efficiency below 1.8 were discarded, and the preparation was repeated. For each sample, a crossing point (quantification cycle) value, which represents the intersection of a fixed threshold above background fluorescence and the amplification curve, was determined by the LightCycler analysis software, v. 4.05. The quantification cycle values were imported to qBase+ software (Biogazelle NV, Zwijnaarde, Belgium; Saremi et al., 2012), and selection of appropriate reference genes and quantification of the data were performed using this software. The genes emerin (*EMD*), hypocalcin-like 1 (*HPCAL1*), and RNA polymerase II (*POL2A*) exhibiting a mean reference target stability M value of 0.344 were identified as optimal reference genes by qBase+ software (Supplemental Table S1, https://doi.org/10.3168/jds.2019-17708).

The geometric mean of the reference gene abundances was used for normalization. Data are presented as the ratio of the copy numbers of genes of interest and the geometric mean of the reference genes' abundances. The RNA of one FOR calf was degraded and could not be used for measurements.

Respiratory Chamber Measurements

For respiratory measurements, animals were temporarily housed in a fully air-conditioned respiratory chamber (Derno et al., 2009) at 21°C from 1000 h on d 2 until 1300 h on d 3 of life and from 1000 h on d 7 until 1300 h on d 8 of life. On d 2, at the start of the respiratory measurements, age was (mean ± SE) 33.7 ± 2.3 h for FOR calves and 31.9 ± 0.7 h for COL calves, respectively. The chambers were littered with straw. The photo period was 13 h light (from 0600 to 1900 h) and 11 h dark. The respiratory measurements started at 1600 h on d 2 and d 7 of life and ended at 1200 h on the following day. Gas exchange of CO_2 and O_2 was recorded at 6-min intervals. Feeding time was at 1700 h on d 2 and 7 and at 0700 h on d 3 and 8. The respiratory quotient (**RQ**) was defined as the quotient between the CO_2 production and the O_2 consumption of calves. Heat production, COX, and FOX were calculated using methods described by Derno et al. (2013). Additionally, an infrared sensor (IS 120; Steinel, Herzbrock-Klarholz, Germany) that was installed in the chamber allowed for registration of the physical activity (standing, lying) of the calves. During feeding, the supporting person wore a face mask connected to the outside of the chamber to avoid falsification of the animals' gaseous exchange.

Statistical Analyses

All results were evaluated using SAS Enterprise Guide 6.1 for Windows (SAS Institute Inc., Cary, NC). For data on blood traits during the first week of life before feed intake (basal blood sampling), the statistical model included the fixed effects of group (colostrum vs. formula) and time (day) as well as their interactions. The model used for analyses of the postprandial effects on d 1 and 9 included the fixed effects of group, day, and time after feeding, as well as their interactions. For evaluation of respiratory measurements, mean values per hour were calculated. For statistical analyses of respiratory measurements and calf activity, the fixed effects of group, day, and time (hourly means), as well as the corresponding interactions, were included in the statistical model. Repeated measures on every calf were considered, using the REPEATED statement of the MIXED procedure and an unstructured type of block diagonal residual covariance matrix. Least squares means (**LSMeans**) and their standard errors were computed for each fixed effect in the models, and all pairwise differences in LSMeans were tested with the Tukey-Kramer procedure. The SLICE statement of the MIXED procedure was used to conduct partitioned analyses of the LSMeans for interactions. Data on gene expression and glycogen concentration in the liver were analyzed using a single-factor variance analysis with group as the fixed effect. Effects and differences were defined as significant at $P < 0.05$ and as a trend at $P <$

0.1. Values are presented as LSMeans ± standard error if not stated otherwise in the text.

RESULTS

Feed Intake, Growth Performance, and Body Temperature

The DMI decreased ($P < 0.05$) in both groups from d 1 to 3 and increased ($P < 0.05$) until d 9 but did not differ between groups (Supplemental Table S2, https://doi.org/10.3168/jds.2019-17708). Calf BW increased ($P < 0.001$) from d 1 to 10 in both groups but did not differ between groups (Supplemental Table S2).

Body temperature increased ($P < 0.05$) until d 3 of life in FOR calves and until d 4 of life in COL calves and thereafter decreased ($P < 0.05$) in both groups until the end of the study (Figure 1). On d 2, 3, and 5, body temperature was higher ($P < 0.05$) in FOR calves than in COL calves.

Metabolic and Endocrine Changes in Blood Plasma

The plasma total protein concentration increased ($P < 0.01$) after feed intake in COL calves but did not change in FOR calves until d 10 and remained higher ($P < 0.05$) in COL calves than in FOR calves throughout the study (Figure 2A). The plasma albumin concentration decreased ($P < 0.01$) after feed intake on d 1 in both groups, showed the lowest concentration in FOR calves on d 7 and in COL calves on d 8 and 9, and tended to be lower ($P < 0.1$) in COL calves than in FOR calves on d 9 (Supplemental Figure S1A, https://doi.org/10.3168/jds.2019-17708). Plasma concentrations of IgG1, IgG2, and IgM increased ($P < 0.05$) in COL calves on d 1 from 120 min after colostrum intake and were higher ($P < 0.05$) throughout the study in COL calves compared with FOR calves, but did not change in FOR calves during the study (Figure 2B–D). Plasma haptoglobin concentration increased ($P < 0.05$) from d 1 to d 2 and after feeding on d 9 only in COL calves, and the overall basal concentrations were higher ($P < 0.05$) in COL calves compared with FOR calves (Figure 2E). Plasma urea concentration increased ($P < 0.05$) until d 3 in both groups, tended to be higher on d 1 and was higher on d 2, but tended to be lower on d 3 and was lower on d 9 in FOR calves compared with COL calves (Figure 2F).

The plasma glucose concentration increased ($P < 0.001$) after feed intake on d 1 and 9 in both groups (Figure 3A). The basal plasma concentration increased ($P < 0.001$) in both groups from d 1 to d 3, decreased
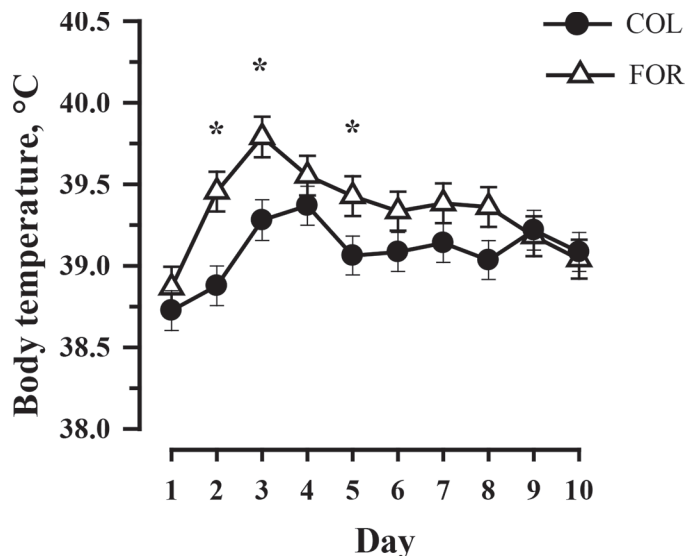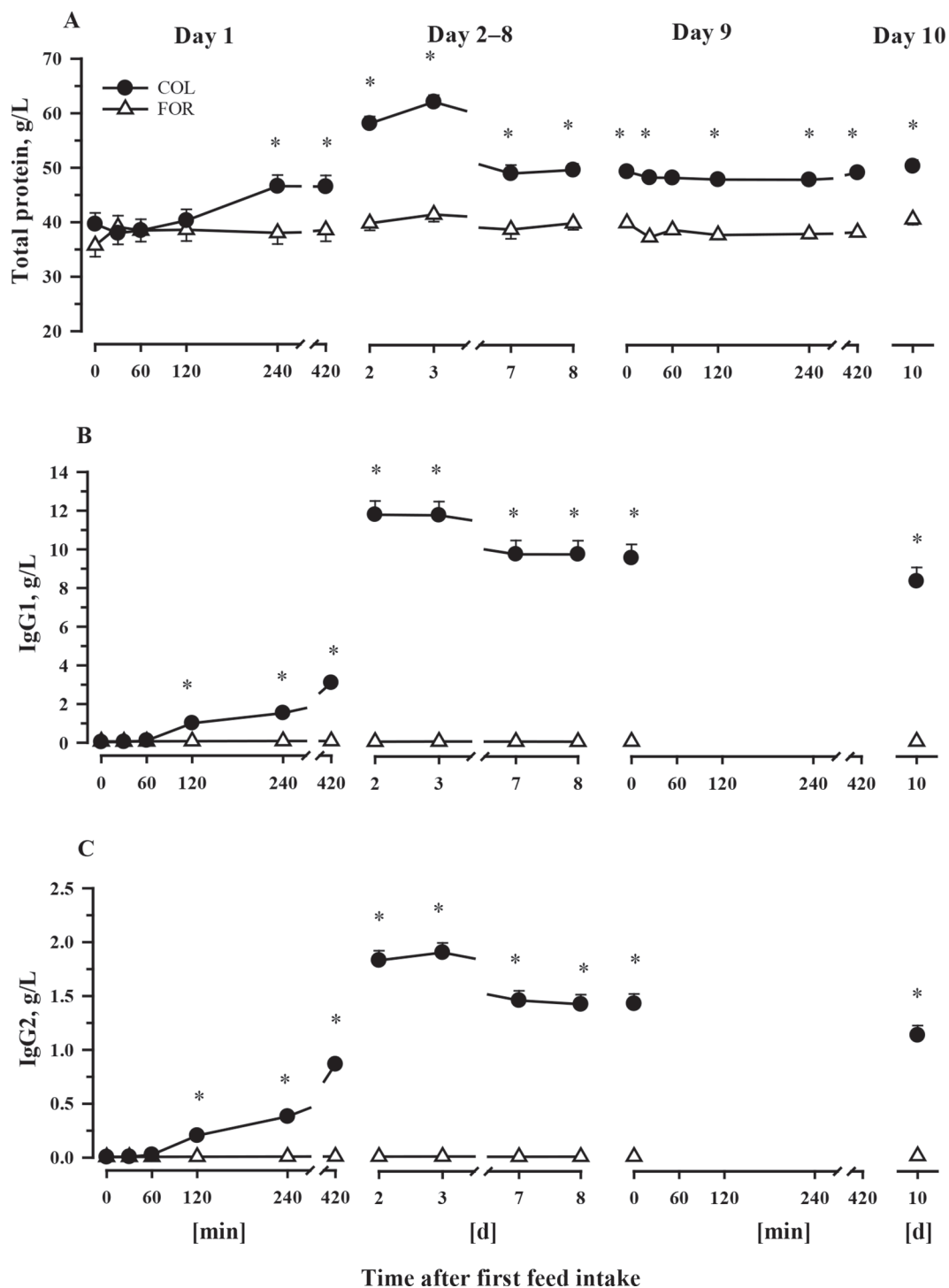

Figure 1. Average daily rectal body temperature during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

afterward ($P < 0.05$), and remained constant until the end of the study. No group effects were observed for plasma glucose. The plasma lactate concentration decreased ($P < 0.05$) from birth until d 8 in both groups and then remained unchanged but showed no group effects (Supplemental Figure S1B, https://doi.org/10.3168/jds.2019-17708). The plasma insulin concentration increased ($P < 0.05$) after feed intake on d 1 and 9 in both groups, but the increase on d 1 was higher ($P < 0.001$) in FOR calves than in COL calves (Figure 3B). On d 2, insulin tended to be higher in FOR calves compared with COL calves ($P = 0.072$). The plasma glucagon concentration increased ($P < 0.05$) after feed intake on d 1 in both groups, but the increase was greater ($P < 0.05$) at 240 and 420 min after feed intake in FOR calves than in COL calves (Figure 3C). From d 3 on, plasma glucagon was higher ($P < 0.05$) in COL calves than in FOR calves until the end of the study. On d 2 and 9, the basal ratio of glucagon to insulin was higher ($P < 0.05$) in COL calves than in FOR calves (Figure 3D). The plasma cortisol concentration decreased ($P < 0.05$) after feed intake on d 1 and 9 in both groups and decreased during the study but did not indicate group effects (Figure 3E).

Plasma NEFA concentration decreased ($P < 0.05$) after feed intake on d 1 and 9, and basal NEFA concentration decreased ($P < 0.05$) from d 1 to 7 and remained unchanged until the end of the study, and the results indicated no diet effect in either group (Figure

4A). The plasma triglyceride concentration increased ($P < 0.01$) in both groups after first feed intake, but the postprandial increase was greater ($P < 0.05$) in FOR calves than in COL calves (Figure 4B). The basal plasma triglyceride concentration increased in both groups until d 3 and again on d 8, was higher ($P <$

Figure 2. Pre- and postprandial plasma concentrations of total protein (A), IgG1 (B), IgG2 (C), IgM (D), haptoglobin (E), and urea (F) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

0.05) on d 3 in COL calves than in FOR calves, and increased ($P < 0.05$) in both groups after feeding on d 9. The plasma cholesterol concentration increased ($P <$ 0.05) after feed intake on d 1 only in FOR calves and was higher ($P < 0.05$) 240 and 420 min after feeding in FOR calves than in COL calves. Plasma cholesterol was
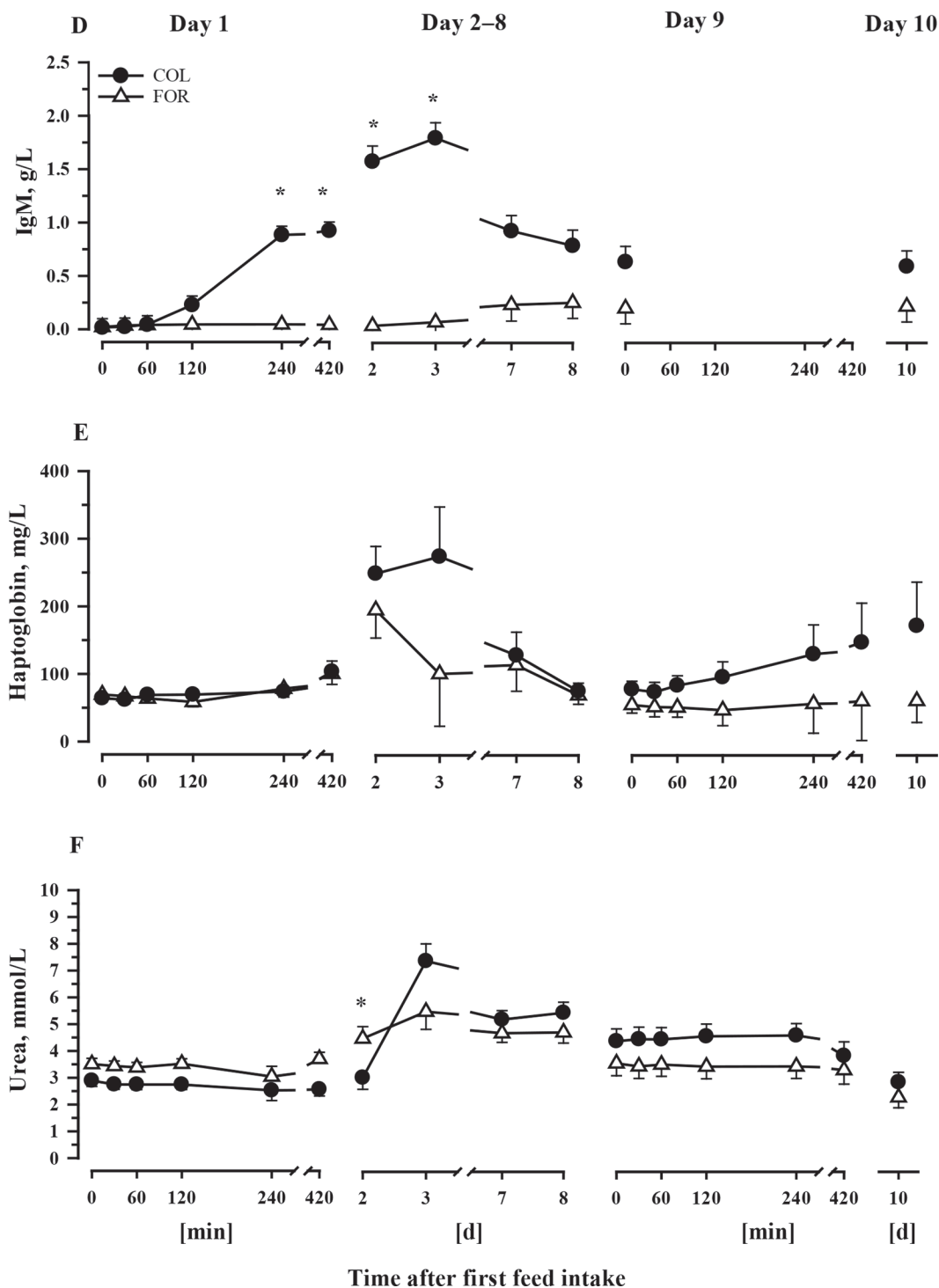
Figure 2 (Continued). Pre- and postprandial plasma concentrations of total protein (A), IgG1 (B), IgG2 (C), IgM (D), haptoglobin (E), and urea (F) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

higher ($P < 0.05$) on d 2 but lower ($P < 0.05$) on d 3 in FOR calves than in COL calves and increased ($P < 0.05$) until d 8 in both groups (Figure 4C).

The plasma GH concentration on d 2 was higher ($P < 0.05$) in COL calves than in FOR calves, and GH varied with time ($P < 0.01$) during the experimental
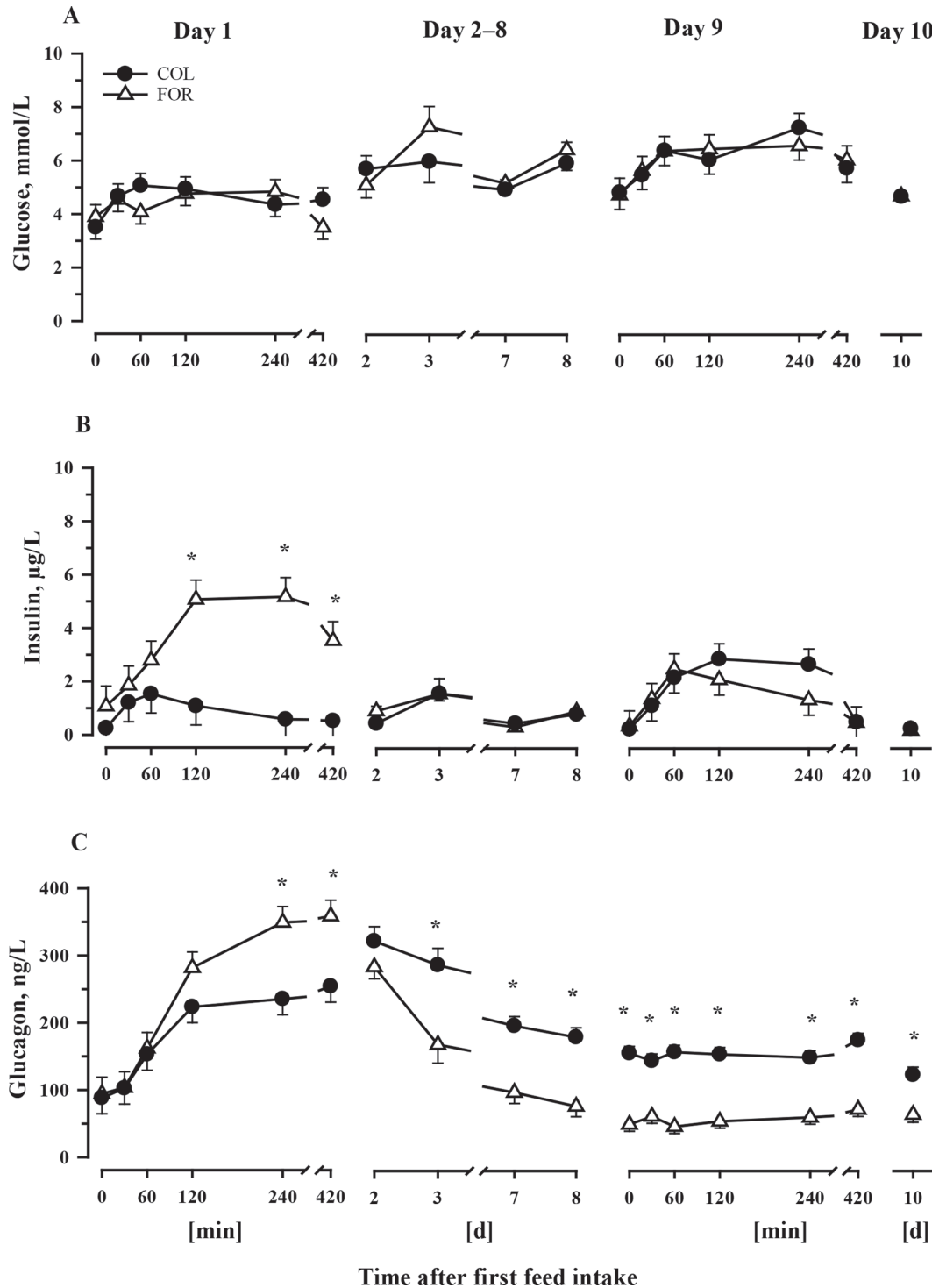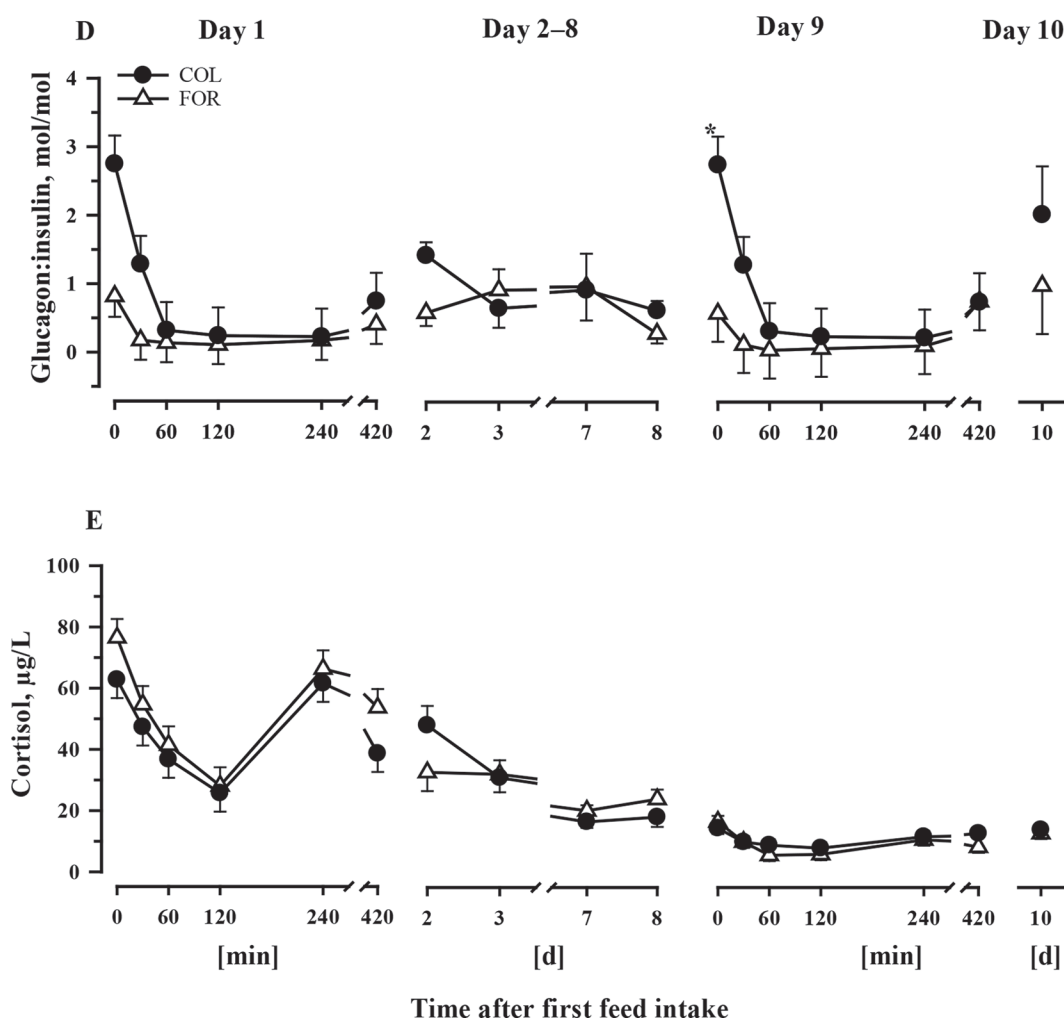

Figure 3. Pre- and postprandial plasma concentrations of glucose (A), insulin (B), glucagon (C), and the glucagon:insulin ratio (D) in blood plasma and plasma concentrations of cortisol (E) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

period but did not indicate further group effects. The basal plasma concentrations of GH were 16.7 ± 2.5 on d 1, 10.3 ± 3.5 for FOR calves and 30.9 ± 3.4 for COL calves on d 2, and 19.2 ± 2.2, 47.2 ± 5.8, 27.1 ± 5.8, 49.9 ± 9.7, and 30.1 ± 5.2 μg/L for d 3, 7, 8, 9, and 10, respectively. The plasma IGF-I concentration decreased ($P < 0.01$) during the first week of life in both groups and was higher ($P < 0.001$) on d 3 in COL calves than in FOR calves (Figure 5A). Plasma concentrations of leptin and adiponectin increased ($P < 0.05$) after feed intake on d 1 only in COL calves, and the concentrations of both hormones were higher ($P < 0.05$) during the whole study in COL calves than in FOR calves (Figure 5B, C). The basal IGFBP-2 plasma concentration increased ($P < 0.05$) from d 7 to 8 in both groups

and was higher ($P < 0.05$) on d 3 in COL calves than in FOR calves (Figure 6A). The basal IGFBP-3 plasma concentration increased ($P < 0.05$) from d 1 to 2 and then decreased ($P < 0.05$) until d 7 in both groups (Figure 6B). Plasma IGFBP-3 ($P < 0.05$) was higher on d 3 and tended to be higher ($P < 0.1$) on d 8 in COL calves than in FOR calves. The basal IGFBP-4 plasma concentration increased ($P < 0.05$) from d 1 to 2 in both groups, but the increase was greater ($P < 0.05$) in COL calves than in FOR calves, decreased in COL calves until d 7 and in FOR calves to d 3, and was higher ($P < 0.05$) in COL calves than in FOR calves from d 2 to 10 (Figure 6C).

Plasma noradrenaline decreased ($P < 0.001$) after feed intake on d 1 and 9 in both groups, and the basal
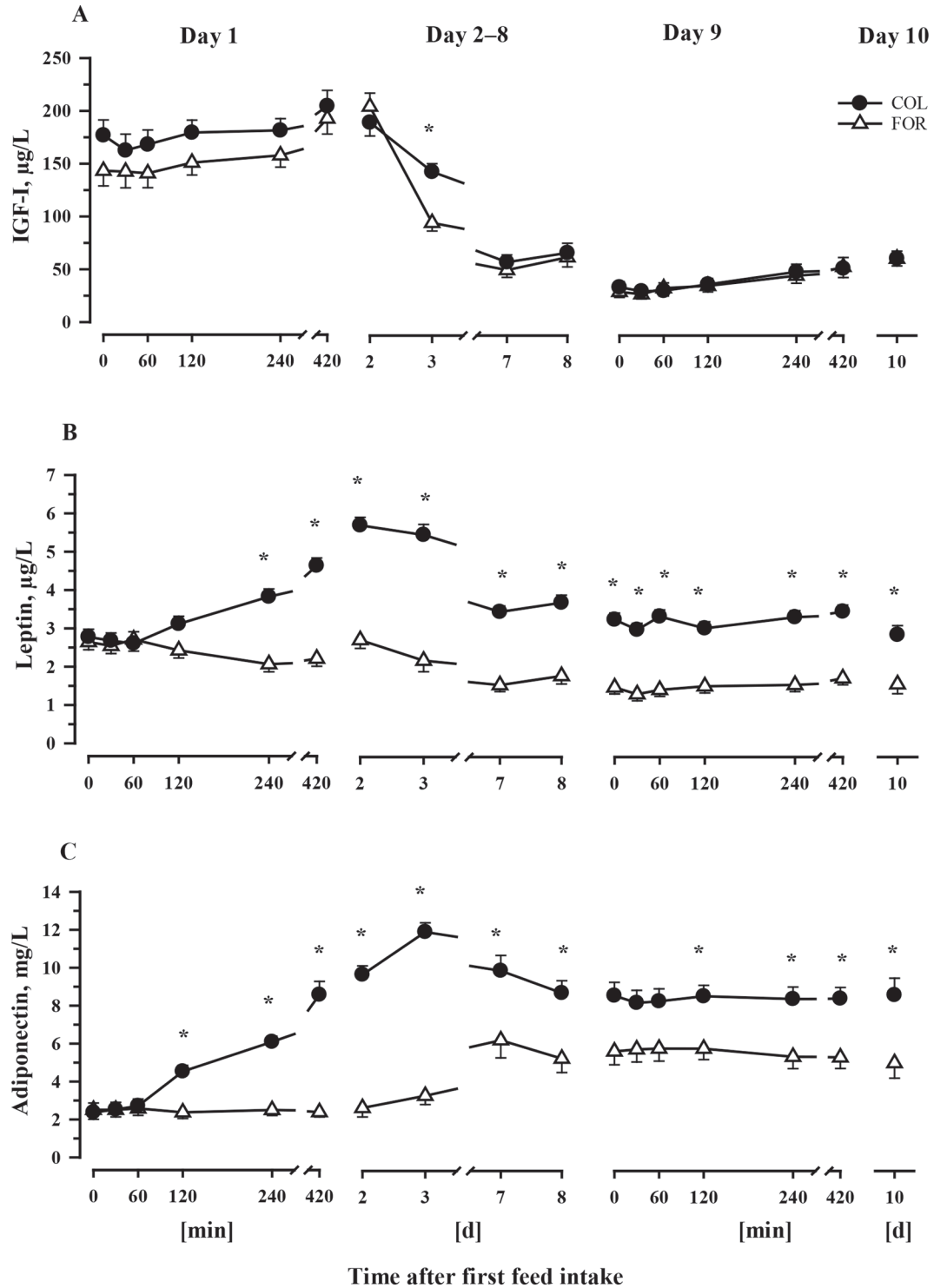

Figure 3 (Continued). Pre- and postprandial plasma concentrations of glucose (A), insulin (B), glucagon (C), and the glucagon:insulin ratio (D) in blood plasma and plasma concentrations of cortisol (E) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

noradrenaline concentration on d 9 was higher ($P <$ 0.001) in FOR- than in COL-fed calves (Figure 7A). The plasma adrenaline concentration variably changed ($P < 0.05$) after feed intake on d 1 but decreased ($P < 0.05$) on d 9 after feed intake and indicated ($P < 0.05$) a higher concentration on d 1 than on d 9 in both
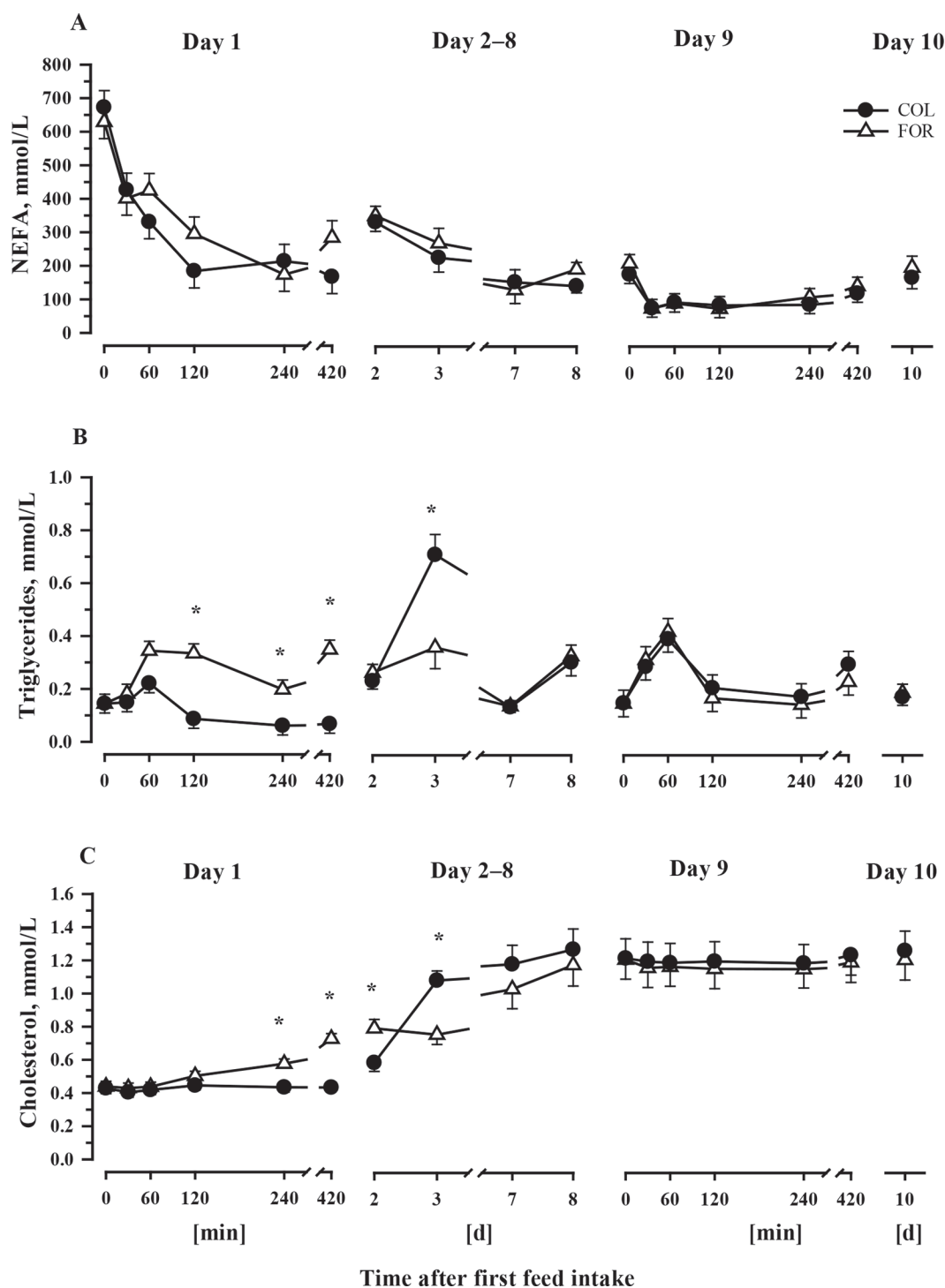
Figure 4. Pre- and postprandial plasma concentrations of nonesterified fatty acids (NEFA; A), triglycerides (B), and cholesterol (C) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

Figure 5. Pre- and postprandial plasma concentrations of IGF-I (A), leptin (B), and adiponectin (C) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as the least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).
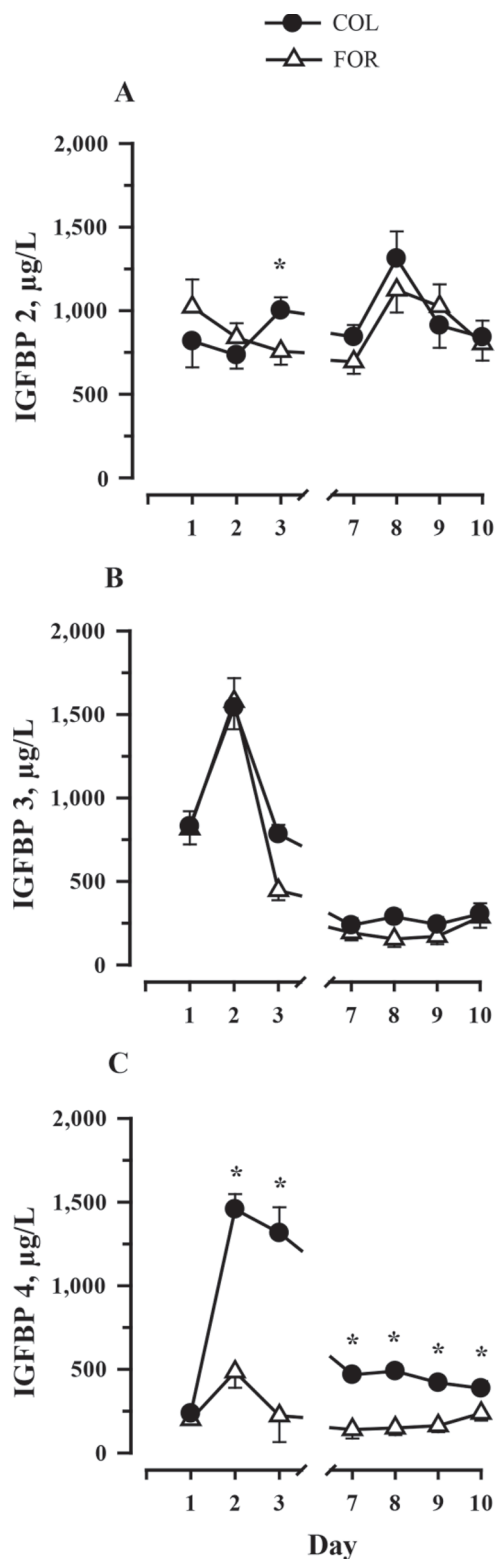
Figure 6. Preprandial plasma concentrations of IGF binding protein (IGFBP)-2 (A), IGFBP-3 (B), and IGFBP-4 (C) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

groups (Figure 7B). Plasma concentrations of T_3 and T_4 decreased ($P < 0.05$) from d 1 to 7 in both groups, and plasma T_3 on d 2 tended to be higher ($P < 0.1$) and on d 3 was higher ($P < 0.05$) in COL calves than in FOR calves (Figure 8A, B).

mRNA Abundance and Glycogen Concentration in Liver

The mRNA abundance of *PCK1* encoding phosphoenolpyruvate carboxykinase 1 was higher in FOR-fed calves than its expression in COL-fed calves (Supplemental Table S3, https://doi.org/10.3168/jds.2019-17708). The mRNA abundance of all other genes investigated herein and the glycogen concentration in liver (Supplemental Table S3) were not affected by group.

Physical Activity and Respiratory Measurements

Both COL- and FOR-fed calves showed increased activity at feeding times on d 2 to 3 and 7 to 8 (Figure 9). Endogenous heat production increased markedly at the time of feeding and decreased thereafter in both groups (Figure 10A). Heat production was higher ($P < 0.05$) in FOR-fed than in COL-fed calves from 1600 h on d 2 until 0100 h on d 3 ($P < 0.05$). Thereafter, no differences were observed between calves from the 2 feeding groups ($P > 0.05$).

We found group (colostrum vs. formula feeding), day, and time (hourly measurements during d 2 to 3 and 7 to 8) interactions in the case of COX ($P < 0.001$; Figure 10B). The COX increased from the time of feeding until 2 to 4 h postprandial (not for FOR calves on d 2) and decreased thereafter. Therefore, the lowest COX was observed 1 to 2 h before feeding time (d 3, 0600 h; d 8, 0500 to 0600 h). However, on d 2, the increase of COX during and after the evening feeding was less pronounced compared with d 7. We found no group effects related to COX between days and at respective hourly measurements within each day on d 2 to 3 or d 7 to 8. A day × time × group interaction was also shown for FOX ($P < 0.001$; Figure 10C). The FOX was lower on d 7 to 8 compared with d 2 to 3 in both feeding groups ($P < 0.05$). The FOX on d 2 to 3 and for FOR calves on d 7 increased before feeding. From feeding until 1 h postprandial, the FOX remained on a plateau and decreased thereafter in the COL calves on d 2 and 3 and in the FOR calves on d 3. The FOX around feeding time on d 2 to 3 was higher at the morning feeding compared with the previous evening feeding ($P < 0.05$). Interestingly, the FOX remained constant for the whole measurement on d 7 to 8 in both groups ($P > 0.05$).
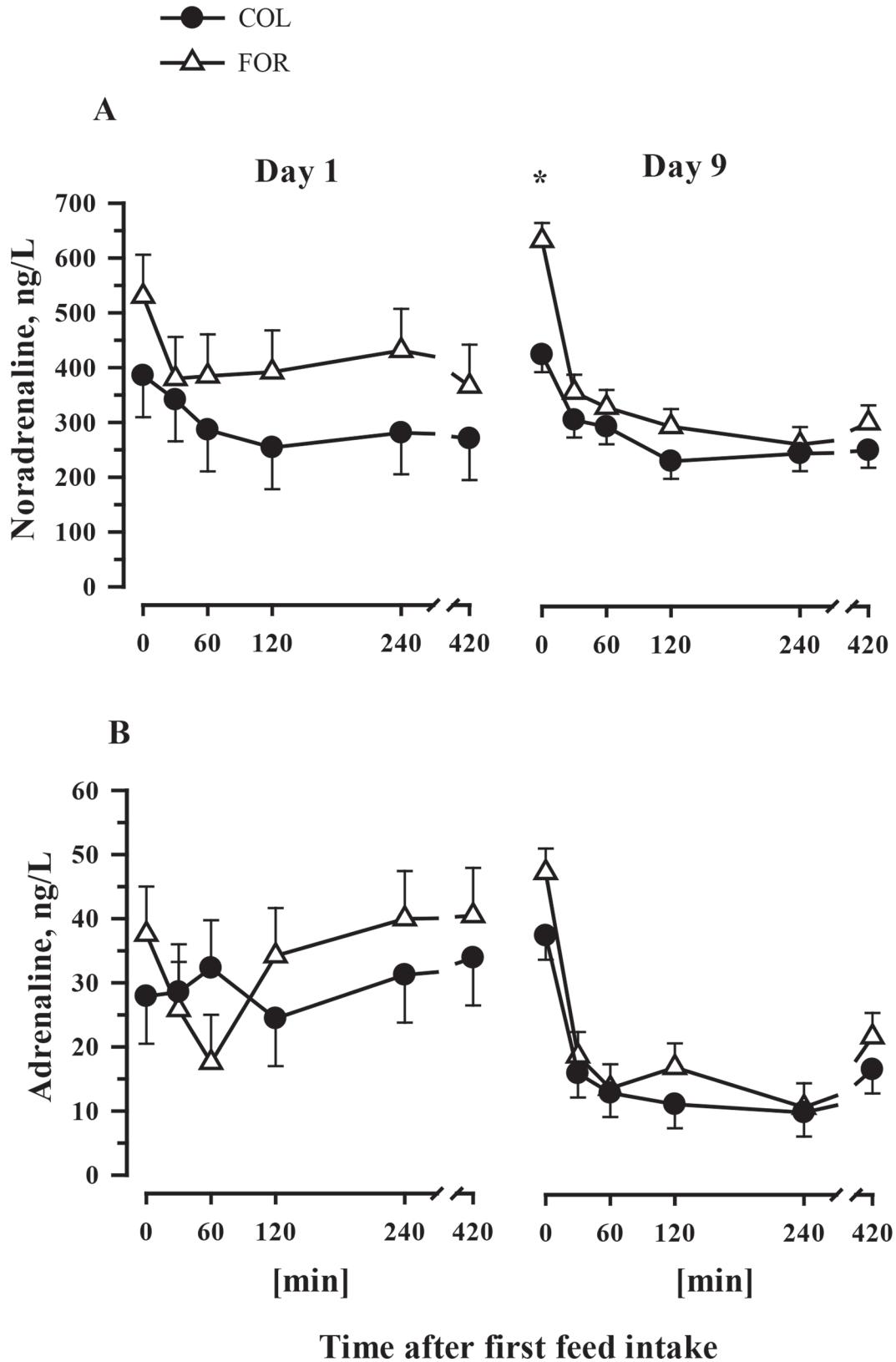
Figure 7. Pre- and postprandial plasma concentrations of noradrenaline (A) and adrenaline (B) on d 1 and 9 in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.001$).
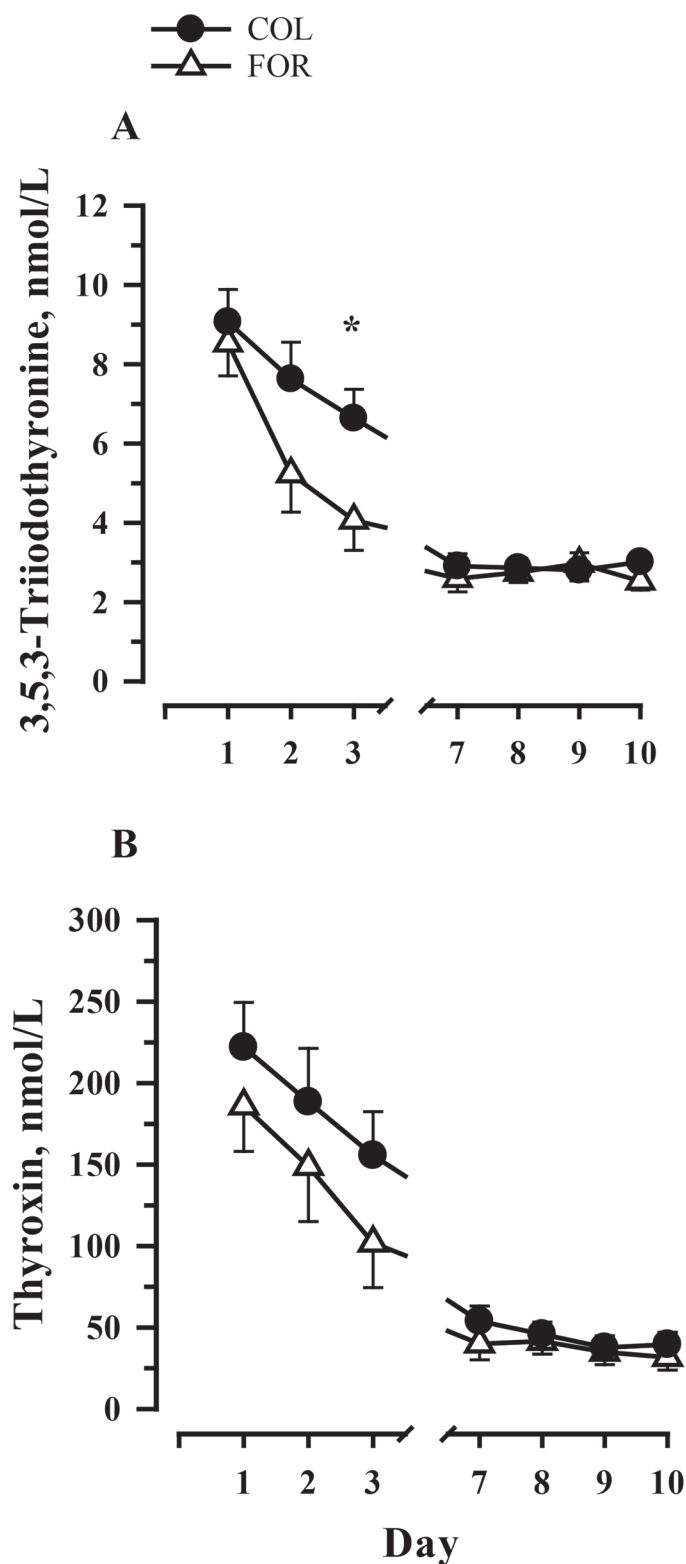
Figure 8. Preprandial plasma concentrations of total triiodothyronine (T_3, A) and thyroxine (T_4, B) during the first 10 d of life in calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life; data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

We found no group effects for FOX at individual time points or for the whole 21-h experimental period.

On d 2 to 3 of life, the RQ increased ($P < 0.05$) compared with the initial level and decreased ($P < 0.01$) from 2200 h in the COL calves (Figure 10D). The lowest RQ was shown between 0600 and 0700 h on d 3 in COL calves. Thereafter, RQ increased ($P < 0.01$) until the end of measurement. The RQ of FOR-fed calves decreased ($P < 0.01$) from 2100 until 0600 h and increased thereafter. On d 7 and 8, a similar sinusoidal development of the RQ was shown over the entire time period in both feeding groups. However, in FOR-fed calves, a marked decrease ($P < 0.001$) in the RQ was observed at 0500 h on d 8. This value was lower compared with the RQ at the time points 2000, 2100, 2300, 0000, 1000, and 1100 h ($P < 0.05$). No differences occurred between the feeding groups considering individual time points or when referring to daily means.

DISCUSSION

The increase in immunoglobulin concentrations in the blood plasma of colostrum-fed calves within the first 24 h after birth reflected an adequate immunoglobulin intake and absorption, which supports the passive immunization of calves (Barrington and Parish, 2001; Godden, 2008). In contrast, immunoglobulin concentrations in formula-fed calves remained low until the end of the experiment. The immunoglobulin intake was also reflected by the total plasma protein concentration, as shown in previous studies (Rauprich et al., 2000; Gruse et al., 2016). The intention of the prophylactic treatments in formula-fed calves was to compensate for the lack of immunological protection by colostrum feeding. Nevertheless, 2 FOR calves got pneumonia and had to be replaced. Apparently, 1 of the 2 calves had swallowed amniotic fluid during the birth process, and formula feeding was probably not the main reason that this calf became sick. However, we cannot rule out the possibility that the second calf contracted pneumonia because it had not been fed colostrum. As known from literature, acute-phase proteins, such as albumin and haptoglobin, indicate inflammatory response and health problems in cattle (Gånheim et al., 2007; Tothova et al., 2014). The remaining calves in the study did not demonstrate strong differences in acute-phase proteins between groups. The trend for elevated plasma haptoglobin and lower albumin concentrations in colostrum-fed calves could not be associated with an impaired health status in these calves. Interestingly, previous findings in neonatal calves indicated higher plasma haptoglobin concentrations with milk-based formula feeding instead of initial colostrum feeding (Gruse et al., 2016). In studies with pigs, it was shown
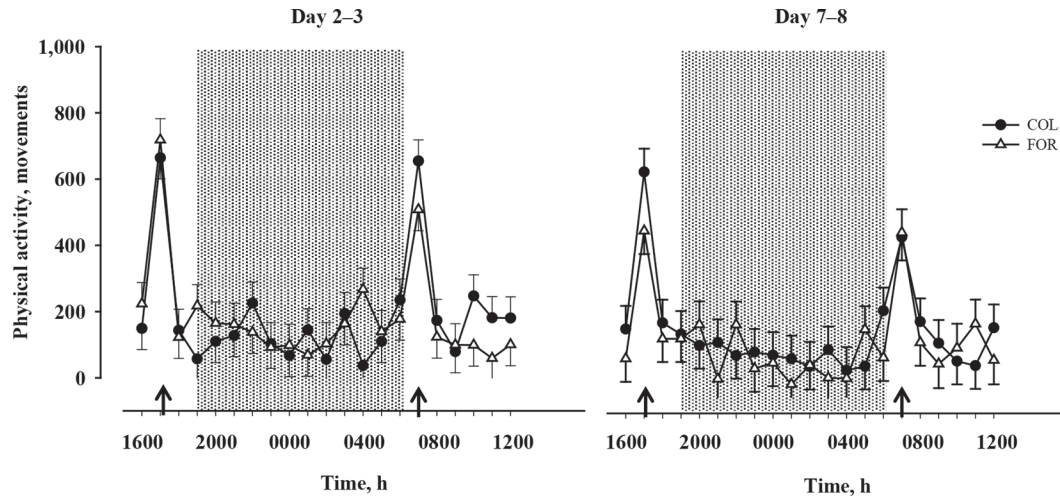
Figure 9. Physical activity on d 2 and 3 and on d 7 and 8 of life of calves fed colostrum (COL, ●) or formula (FOR, △) for the first 2 d of life. Activity was measured in respiration chambers during respiratory measurements. Shaded areas indicate the dark periods. Arrows indicate times of feeding. Data are presented as least squares means ± SE (n = 9 per group).

that haptoglobin is absorbed from colostrum and that endogenous haptoglobin synthesis is stimulated by colostrum feeding (Hiss-Pesch et al., 2011). In the present study, we found no indication of haptoglobin absorption after first colostrum intake.

The postprandial time changes of IGF-I in blood plasma after first colostrum feeding in the present study support previous findings that indicated no IGF-I absorption from colostrum (Vacher et al., 1995; Hammon and Blum, 1997; Hammon et al., 2012). The IGF-I status of calves is more affected by energy and protein intake than by colostrum intake (Frieten et al., 2018; Haisan et al., 2018). However, postprandial time changes in plasma leptin and adiponectin after first feed intake behaved differently—both hormones increased after first colostrum feeding—showing the same postprandial time pattern as that observed for plasma concentrations of total protein and immunoglobulins. Both hormones are highly concentrated in first colostrum (Kesser et al., 2015, 2017), and the absorption of adiponectin from first colostrum was recently shown in neonatal calves (Kesser et al., 2015). Leptin absorption from colostrum was less clear in previous studies, but an elevated plasma concentration of leptin was also associated with colostrum feeding (Blum et al., 2005; Schäff et al., 2014; Kesser et al., 2017). Absorption of colostral leptin occurs in rats and humans (Szymeczko et al., 2009; Woliński et al., 2014; Palou et al., 2018). Previous studies indicated lower leptin and adiponectin concentrations in milk or milk-based formulas than in colostrum (Kesser et al., 2015, 2017). The lack of time changes in leptin and adiponectin in blood plasma of formula-fed calves on d 1 of life makes it very clear

that the increase in leptin and adiponectin plasma concentrations after first colostrum feeding resulted from intestinal absorption of both hormones and that both hormones behaved differently than colostral IGF-I. Higher plasma concentrations of leptin and adiponectin were observed until the end of the study on d 10 of life. The differences in plasma leptin and adiponectin at the end of the study most likely do not result from different endogenous production due to variable body fat in COL and FOR calves. The body fat content in neonatal calves is low; for instance, percentage of perirenal fat in 2-wk-old calves is about 0.1 to 0.2% of carcass weight but is about 1.1 to 1.7% of carcass weight in dairy cows (Drackley et al., 2014; MacGhee et al., 2017).

The question remains whether the absorbed leptin and adiponectin are of physiological relevance in neonatal calves. Both hormones are known for their improvement of insulin sensitivity (Havel, 2002; Yamauchi and Kadowaki, 2013; Palou et al., 2018). Interestingly, insulin concentrations in blood plasma on the first day of life were much greater after formula feeding than after colostrum feeding, whereas the plasma glucose concentration was similar between the feeding groups. However, lactose content in the formula was greater than in colostrum, and therefore lactose intake from formula was greater than from colostrum, which may partly explain the greater insulin release after first feeding in FOR than in COL calves. In addition, it is possible that the colostral leptin and adiponectin in COL calves may have supported insulin action on glucose homeostasis and may have contributed to the lower plasma insulin release in colostrum- than in formula-fed calves after first feed intake. Although we have not
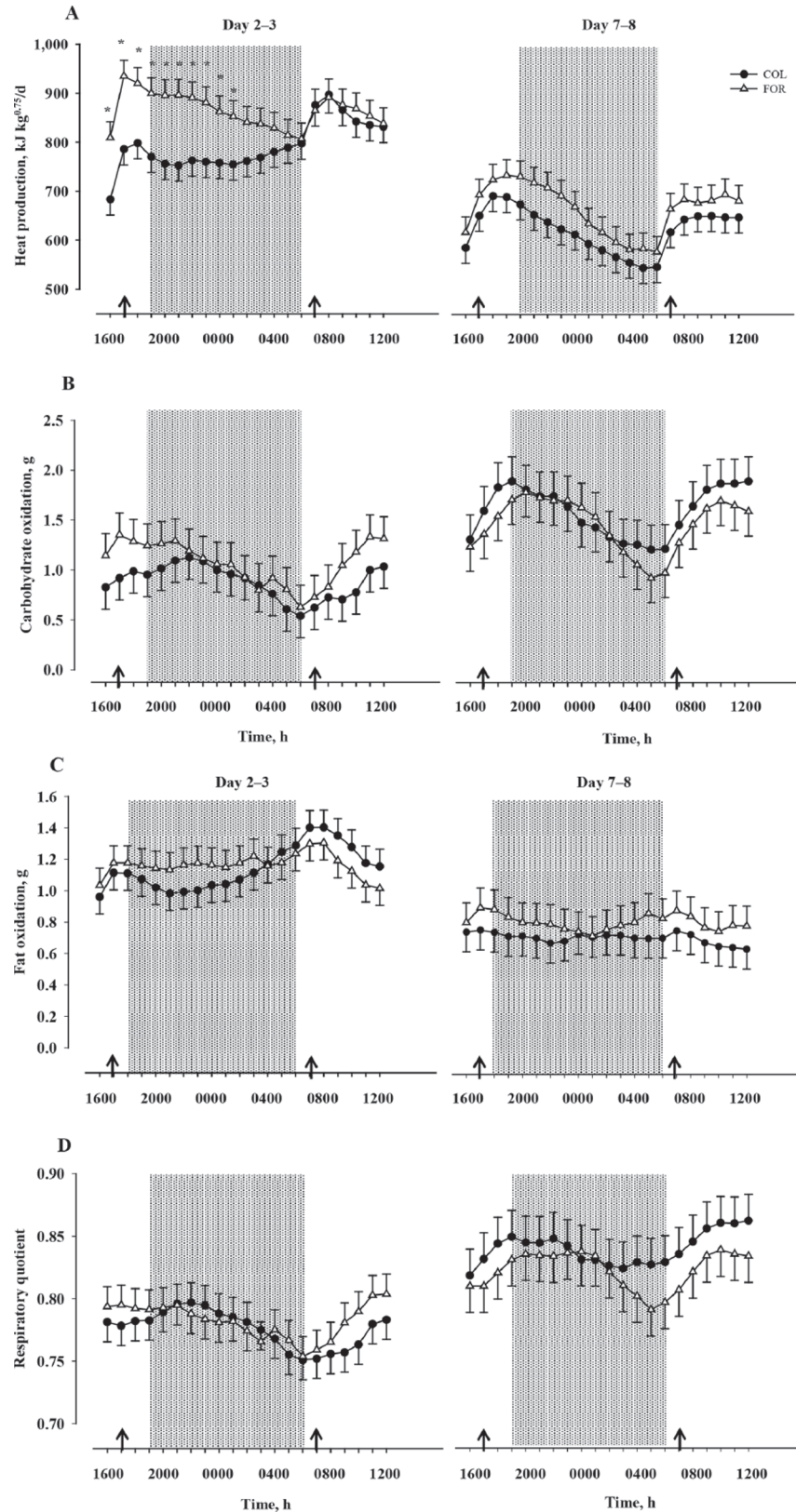
Figure 10. Heat production (A), carbohydrate oxidation (B), fat oxidation (C), and respiratory quotient (D) on d 2 to 3 and 7 to 8 in calves fed colostrum (COL, ●) or formula (FOR, Δ) for the first 2 d of life. Shaded areas indicate the dark periods. Arrows indicate feeding times. Data are presented as least squares means ± SE (n = 9 per group); *designates significant differences between feeding groups ($P < 0.05$).

investigated the effects of diet on insulin sensitivity and pancreatic release in 1-d-old calves using glucose clamp studies, we speculate that the elevated plasma insulin concentration in formula-fed calves on d 1 of life was partly the consequence of impaired insulin regulation due to the low leptin and adiponectin status of formula-fed calves. Alternatively, leptin may reduce plasma insulin in colostrum-fed calves by inhibiting pancreatic insulin release (Houseknecht et al., 1998).

With the exception of d 3 of life, plasma concentrations of IGF-I as well as of IGFBP-2 and -3 did not differ between groups. Therefore, the intake of IGF-I and IGFBP from colostrum did not contribute to systemic IGF-I and IGFBP measured in blood plasma (Blum and Hammon, 2000; Blum and Baumrucker, 2008; Meyer et al., 2017). Differences in systemic IGF-I and IGBP are more related to changes in energy and protein intake (Schäff et al., 2016; Frieten et al., 2018; Haisan et al., 2018). Because the nutrient supply was the same in formula- and colostrum-fed calves, IGF-I and IGFBP-2 and -3 plasma concentrations were similar in both groups. Interestingly, the plasma concentration of IGFBP-4 distinctly increased after colostrum feeding and therefore behaved differently between feeding groups, which was not the case for IGFBP-2 or -3. Whether elevated plasma IGFBP-4 indeed resulted from colostral IGFBP-4 absorption cannot be determined from the present study, because we did not measure the IGFBP-4 plasma concentration immediately after colostrum and formula feeding on d 1 of life. The concentration of IGFBP-4 is higher in colostrum than in mature milk (Sejrsen et al., 2001; Blum and Baumrucker, 2008; Meyer et al., 2017). Whether colostral IGFBP-4 has an influence on systemic IGFBP-4 availability in neonatal calves and affects neonatal development needs further investigation.

Data from respiratory measurements indicated greater heat production on d 2 and 3 than on d 7 and 8 and at feeding times in both groups. Greater heat production at birth was probably the consequence of the metabolic activity of the brown fat tissue that decreased with time (Vermorel et al., 1983). The thyroid hormones stimulate thermogenesis, and the decrease in plasma T_3 and T_4 during the neonatal period is in line with the lower heat production at 7 and 8 d of age (Silva, 2006; Hammon et al., 2012; Schäff et al., 2014). The greater heat production at feeding times might be a result of greater physical activity and, in addition, of stimulating digestive processes in the gastrointestinal tract at that time (Vermorel et al., 1983). A greater metabolic heat production in formula-fed than in colostrum-fed calves during the first measurements on d 2 and 3 corresponded with an elevated body temperature in formula-fed calves on d 2 and 3. Although a trend oc-

curred for higher body temperature in formula-fed than in colostrum-fed calves on d 8 of life, metabolic heat production was only numerically higher in formula-fed calves on d 7 and 8. Because of the prophylactic treatments in formula-fed calves, no clinical signs of disease appeared in this group, and the higher metabolic heat production may explain at least part of the elevated body temperature.

Metabolic heat production significantly differed when calves were fed either colostrum or formula but not when MR was provided to all calves and, surprisingly, was greater in formula-fed than in colostrum-fed calves. Interestingly, adiponectin decreases thermogenesis in mice (Qiao et al., 2014). Therefore, the elevated adiponectin concentration in the blood plasma of colostrum-fed calves may have contributed to the lower heat production after colostrum feeding on d 2 of life. On the other hand, plasma concentrations of T_3 and leptin were higher in colostrum-fed than in formula-fed calves on d 2 and 3. Because thyroid hormones, leptin, and the sympathetic nervous system are supposed to stimulate thermogenesis and heat production (Döring et al., 1998; Houseknecht et al., 1998; Havel, 2002; Silva, 2006), the lower heat production on d 2 in colostrum-fed than in formula-fed calves is not in agreement with the elevated plasma T_3 and leptin concentrations in COL calves. The plasma concentrations of adrenaline and noradrenaline decreased after feeding but were similar on d 1 between groups. The reasons for this discrepancy in heat production and endocrine changes in calves due to different milk feedings are presently unknown. Considering that colostrum feeding stimulates anabolic processes in calves (Hammon et al., 2012, 2013), the lack of colostrum intake may have impaired the start of postnatal anabolic metabolism in formula-fed calves and may have led to metabolic processes that resulted in elevated heat production. The elevated plasma urea concentration in formula-fed calves compared with colostrum-fed calves on d 1 and 2 may support this assumption by indicating enhanced amino acid degradation and probably less protein synthesis in formula-fed calves. Colostrum feeding clearly supports anabolic processes and protein synthesis in neonatal pigs (Reeds et al., 2000). Elevated plasma urea concentrations in formula-fed compared with colostrum-fed calves with the same protein intake were also reported previously in neonatal calves, indicating less use of amino acids for protein synthesis and elevated amino acid degradation and oxidation (Rauprich et al., 2000; Steinhoff-Wagner et al., 2011).

Measurements of COX and FOX in the respiratory chambers on d 2 and 3 and d 7 and 8 indicated time changes with respect to feeding but did not reveal group effects. Carbohydrate oxidation increased and

FOX decreased postprandially, but FOX increased at the end of the feeding intervals (i.e., before subsequent feed intake) in both groups. This pattern of substrate oxidation relative to feed intake is known from mice (Flatt, 1991) and has also been described in dairy cows (Derno et al., 2013), and it resulted in an increase in the RQ after feed intake and lowest RQ at the end of the feeding interval. The mean RQ increased from d 2 and 3 to d 7 and 8, indicating that calves of both groups utilize more carbohydrates and less fat at the end of the first week of life. One reason for this change might be the elevated lactose content in MR compared with colostrum and formula on d 1 and 2, respectively. Therefore, different feeding for the first 2 d had no prolonged effects on substrate utilization and heat production in neonatal calves. On the other hand, data from respiratory measurements indicated comparable energy supplies of both groups during the first week of life. This finding is also supported by plasma NEFA concentration, which did not differ between groups and indicated no difference in body fat mobilization between groups.

Calves were fed colostrum or formula with similar crude fat contents. However, colostrum contains much more cholesterol than mature milk (Ontsouka et al., 2016), but cholesterol was not measured in formula. Surprisingly, postprandial plasma concentrations of triglyceride and cholesterol were greater after formula than after colostrum intake on d 1. The relationship of triglyceride and cholesterol plasma concentrations changed with age. Higher concentrations of both metabolites were measured on d 3 in colostrum-fed than in formula-fed calves. Most studies in neonatal calves indicated an elevated triglyceride and cholesterol status after colostrum feeding compared with either formula or MR feeding immediately after birth (Hammon and Blum, 1998; Kühne et al., 2000; Rauprich et al., 2000). The reasons for these contradictory findings are presently unknown, but the differences may be partly the consequence of variable fat sources in the formulas (as a replacement of colostrum) and MR of the previous studies. Replacement of colostrum by formula or MR may affect cholesterol homeostasis and plasma cholesterol concentration in neonatal calves due to changes in cholesterol absorption, endogenous synthesis, and utilization (Ontsouka et al., 2016), as reported among neonatal pigs (Ronis et al., 2011). More studies are needed to clarify the importance of colostrum feeding and replacement of colostrum for cholesterol status in newborn calves.

The decrease in plasma cortisol after feeding and during the neonatal period has previously been reported (Hammon and Blum, 1998; Kühne et al., 2000;

Rauprich et al., 2000). In addition, the postprandial decrease in noradrenaline and adrenaline was also described previously (Gruse et al., 2015). With the exception of plasma noradrenaline on d 9 before feeding, no effects due to different milk diets for the first 2 d of life were observed. The higher plasma concentration of noradrenaline on d 9 cannot be explained by differences in metabolic or physical stress or housing between the groups and requires further verification. In contrast, plasma glucagon increased after the first feeding to a greater extent in formula-fed than in colostrum-fed calves. The greater glucagon rise on d 1 of life in formula-fed than in colostrum-fed calves was observed in a previous study (Hammon et al., 2003) and was probably a response of the elevated insulin release in formula-fed calves. Glucagon release is stimulated by insulin in adult and neonatal cattle (Brockman and Laarveld, 1986; Hammon et al., 2012; Zarrin et al., 2015). From d 3 on, plasma glucagon was higher in colostrum-fed than in formula-fed calves. An elevated plasma glucagon concentration due to colostrum feeding on first day of life has been observed in some (Hammon and Blum, 1998; Gruse et al., 2015) but not all studies with neonatal calves (Rauprich et al., 2000; Hammon et al., 2003; Steinhoff-Wagner et al., 2011). There is no clear pattern of glucagon changes during the first week of life with respect to colostrum versus formula feeding for first 2 d of life. In addition, the lower hepatic expression of *PCK1* on d 10 of life does not fit with the elevated plasma glucagon concentration and glucagon-to-insulin ratio in colostrum-fed calves. The *PCK1* gene codes for the cytosolic form of phosphoenolpyruvate carboxykinase, which is a rate-limiting enzyme for gluconeogenesis, stimulated by glucagon (Pilkis and Granner, 1992), and its gene expression depends on neonatal maturation in calves (Hammon et al., 2012). However, neonatal gluconeogenesis is not affected by colostrum versus formula feeding in calves (Scheuer et al., 2006; Steinhoff-Wagner et al., 2011). Overall, the importance of the postnatal changes in plasma glucagon requires further investigation.

CONCLUSIONS

Measurements in the respiratory chamber indicate an unexpectedly elevated heat production when calves were fed a milk-based formula instead of colostrum for the first 2 d after birth. However, the effects on heat production did not continue during the first week of life. Carbohydrate and fat oxidation did not differ according to colostrum or formula feeding but changed with age during the neonatal period. The absorption of colostral leptin and adiponectin might affect insulin

sensitivity in neonatal calves, but further studies are needed to substantiate the influence of colostral leptin and adiponectin on insulin sensitivity after birth.

ACKNOWLEDGMENTS

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