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Endocrine and metabolic changes in transition dairy cows are affected by prepartum infusions of a serotonin precursor

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ABSTRACT

Serotonin (5-HT) has been shown to be involved in calcium homeostasis, modulating calcium concentration in blood. In addition, 5-HT participates in a variety of metabolic pathways, mainly through the modulation of glucose and lipid metabolism. The hypothesis of the present study was that the prepartum administration of 5-hydroxy-L-tryptophan (5-HTP), a 5-HT precursor, would affect endocrine systems related to calcium homeostasis, and interact with other endocrine and metabolic pathways during the transition period. In this study, 20 Holstein dairy cows were randomly assigned to 2 experimental groups. Both groups received a daily i.v. infusion of 1 L of either 0.9% NaCl (control group; n = 10) or 0.9% NaCl containing 1 mg of 5-HTP/kg of BW (5-HTP group, n = 10). Infusions started d 10 before estimated parturition date and ended the day of parturition, resulting in a minimum of 4 d of infusion (8.4 ± 0.7 d of infusion). Until parturition, blood samples were collected before the daily infusions, and postpartum daily until d 7, and on d 30. Plasma concentrations of parathyroid hormone (PTH) were transiently increased at parturition and on d 1 in control cows. In the 5-HTP group PTH remained unchanged. The concentration of pyridinoline (PYD), an established marker for calcium release from the bone to the bloodstream, increased on d 1 postpartum only in the 5-HTP group. In control cows, PYD concentrations did not change on d 1 postpartum. Melatonin concentrations were slightly but significantly increased in the 5-HTP group compared with the control group. Insulin concentrations decreased in both groups postpartum. Before parturition, leptin concentrations decreased in both groups and remained at this level until d 30 postpartum. Plasma IgG concentrations decreased in both groups on d −1 postpartum. Haptoglobin increased in both groups on d −1 and remained at this level until d 7 postpartum. No differences between groups were observed for insulin, glucagon, IgG, leptin, adiponectin, and haptoglobin concentrations. The results obtained in the present study evidenced that 5-HT is regulating calcium homeostasis independent of PTH. The lack of treatment effects on IgG and on other hormones and metabolites indicates that 5-HTP did not affect these other metabolic pathways and the IgG concentration during the transition period.

Key words: serotonin, hypocalcemia, metabolism, 5-hydroxy-L-tryptophan, parathyroid hormone

INTRODUCTION

The transition period is considered most challenging and critical in relation to the dairy cow's health status during the lactation cycle (Kessel et al., 2008). Major physiological, nutritional, metabolic, and immunological changes take place due to the onset of milk secretion, concomitantly with parturition (Drackley, 1999; Gross et al., 2011). The metabolic load makes cows susceptible to production diseases such as metritis, ketosis, mastitis, or hypocalcemia during the transition period (Fleischer et al., 2001; Van Knegsel et al., 2014). Serotonin (5-hydroxytryptamine, **5-HT**), a monoamine synthesized from the AA L-tryptophan, is synthesized by the central nervous system, but also by various peripheral tissues including the mammary gland (Lauder, 2004). Serotonin has been demonstrated to be an autocrine regulator of mammary gland metabolism, including calcium homeostasis (Hernandez et al., 2012; Laporta et al., 2015) and milk synthesis (Matsuda et al., 2004). Recently, Weaver et al. (2016) and Hernández-Castellano et al. (2017) demonstrated that the infusion of the 5-HT precursor 5-hydroxytryptophan (**5-HTP**) during the last days before parturition improved blood calcium concentrations around parturition. Additionally, 5-HT has been shown to influence several metabolites related to glucose and lipid metabolism such as glucose, insulin, triglyceride, cholesterol, and fatty acid concentrations in mice (Sugimoto et al.,

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1990; Watanabe et al., 2010) and sheep (Watanabe et al., 2014). Moreover, 5-HT promotes the proliferation and activation of B cells in mice (Iken et al., 1995), and therefore the IgG concentration could also be affected by the increased 5-HT concentration in blood. Similar effects have so far not been demonstrated in dairy cows. Based on the known functions of 5-HT, we have tested the hypothesis that the administration of 5-HTP prepartum will affect different endocrine factors related to calcium homeostasis and will interact also with other immune, endocrine, and metabolic pathways during the transition period.

MATERIALS AND METHODS

In this study, animal health status was monitored and animals did not show any symptoms of illness. This trial was approved by the Cantonal Committee for Animal Experiments (Canton of Fribourg, Switzerland), and all experimental procedures followed the Swiss law of animal protection.

Animals and Treatments

Twenty multiparous Holstein dairy cows from the experimental herd of the Agroscope Institute for Livestock Science research farm (Posieux, Switzerland) were used in this study. The day before the initiation of the infusions (**B**), cows were fitted with indwelling i.v. catheters (Abbocath-T, Hospira Deutschland GmbH, Munich, Germany) with a length of 14 cm and a diameter of 14 G in a jugular vein. Both groups received a daily i.v. infusion of 1 L over 1 h (0700–0800 h) of either 0.9% NaCl (control group) or 0.9% NaCl containing 1 mg of 5-HTP/kg of BW (5-HTP group) from d −10 before the predicted parturition date until parturition. As described by Hernández-Castellano et al. (2017), this 5-HTP dosage caused an increase in serum 5-HT concentration from 5.49 μmol/L up (5-HT concentration B) to 12.94 μmol/L on d −4 prepartum, and maintaining 5-HT concentrations at elevated level until d 5 postpartum (9.75 μmol/L). Blood samples were collected every morning before the infusions, and postpartum daily until d 7. An additional sample was collected on d 30 postpartum. Cows were fed according to the guidelines published by Agroscope (2015). Briefly, cows received hay ad libitum (DM content, 890 g/kg of fresh matter, on a DM basis, consisting of 125 g of CP/kg, 235 g of crude fiber/kg, 14.6 g/kg of calcium, and 5.7 MJ of NE_L/kg) and had free access to water. In addition, cows received a concentrate supplementation (6 MJ of NE_L/kg of DM and 5 g of calcium/kg) pre- and postpartum (0.5 and 2.5 kg per day and cow, respectively). In addition, cows were supplemented with a vitamin/mineral premix providing 2.5 g of calcium/d prepartum and 31.8 g of calcium/d postpartum.

Sample Collection

Blood samples were taken from the jugular catheter (0700 h) and placed into tubes for serum collection as well as tubes for plasma collection, containing 3K-EDTA. During the prepartum period, blood samples were always collected before the daily infusion of either control or treatment solution. Blood was stored either on wet ice (plasma tubes) or at room temperature (serum tubes) until centrifugation at 2,500 × *g* for 20 min at 4°C to obtain either plasma or serum, which was stored at −80°C until analyses.

Variables Measured in Plasma and Serum

Plasma insulin concentration was measured by RIA as described by Vicari et al. (2008). Plasma glucagon concentration was measured by using a commercial RIA kit (catalog no. GL-32K, Millipore AG, Zug, Switzerland). Commercial ELISA kits were used to determine melatonin (catalog no. RE54021, IBL-International, Hamburg, Germany) and parathyroid hormone (**PTH**) in plasma (catalog no. 60–3500, Immutopics, Athens, OH). Serum pyridinoline (**PYD**) was measured by ELISA using the MicroVue PYD EIA kit (catalog no. 8019, Quidel MicroVue, San Diego, CA). Serum adiponectin concentration was measured by ELISA as described by Kesser et al. (2015). Serum leptin concentration was measured by ELISA as described by Sauerwein et al. (2004), and haptoglobin (**Hp**) concentration was measured in serum by enzyme immunoassay as described by Hiss et al. (2009). The serum used had been calibrated against a standard obtained from a European Union Concerted Action on the standardization of animal acute phase proteins (QLK5-CT-1999–0153; Skinner, 2001). The parathyroid hormone-related protein (**PTHrP**) concentrations were measured using the Active PTHrP IRMA kit (#DSL8100, Beckman Coulter GmbH, Sinsheim, Germany). Total IgG concentration in plasma was measured using a commercial ELISA kit specific to bovine IgG (Bethyl Laboratories, Montgomery, TX) with some modifications as described by Lehmann et al. (2015). Total serum calcium concentration was determined using a commercial kit from Diatools (DIA00461, Diatools AG, Villmergen, Switzerland).

Statistical Analysis

Results are presented as means ± standard error of the mean. Statistical analyses were performed by using