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Increased serum serotonin improves parturient calcium homeostasis in dairy cows

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ABSTRACT

Hypocalcemia in dairy cows is caused by the sudden increase in calcium demand by the mammary gland for milk production at the onset of lactation. Serotonin (5-HT) is a key factor for calcium homeostasis, modulating calcium concentration in blood. Therefore, it is hypothesized that administration of 5-hydroxy-L-tryptophan (5-HTP), a 5-HT precursor, can increase 5-HT concentrations in blood and, in turn, induce an increase in blood calcium concentration. 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 (C 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 the estimated parturition and ceased the day of parturition, resulting in at least 4 d of infusion (8.37 ± 0.74 d of infusion). Until parturition, blood samples were collected every morning before the infusions, after parturition samples were taken daily until d 7, and a final sample was collected on d 30. Milk yield was recorded during this period. No differences between groups were observed for blood glucose, magnesium, and β-hydroxybutyrate. Cows receiving the 5-HTP infusion showed an increase in fatty acid concentrations from d −3 to −1 before parturition. Serum 5-HT concentrations were increased at d −4 related to parturition until d 5 postpartum in the 5-HTP group compared with the C group. In addition, cows from the 5-HTP group had increased 5-HT concentrations in colostrum, but not in mature milk, on d 7 postpartum. Serum calcium concentrations decreased in both groups around parturition; however, calcium remained higher in the 5-HTP group than in controls, with a significant difference between groups on d 1 (1.62 ± 0.08 vs. 1.93 ± 0.09 mmol/L in control and 5-HTP groups, respectively) and d 2 (1.83 ± 0.06 vs. 2.07 ± 0.07 mmol/L in control and 5-HTP groups, respectively). Additionally, colostrum yield (first milking) was lower in the 5-HTP group compared with the C group, but without consequences on colostrum IgG concentrations. Milk yield did not differ between groups during the rest of the experiment. The study data were consistent with the concept that infusion of 5-HTP to dairy cows increases blood 5-HT concentrations, which in turn is a significant regulatory component in the chain of effectors that affect calcium status around parturition, hence the occurrence of clinical or subclinical hypocalcemia.

Key words: serotonin, hypocalcemia, calcium, 5-hydroxy-L-tryptophan

INTRODUCTION

Hypocalcemia (**HC**) is a frequent problem in parturient dairy cows (Oetzel, 1988). According to Reinhardt et al. (2011), in countries with high-yielding cows the incidence of clinical hypocalcemia (calcium concentration <1.5 mmol/L) is estimated to be 5%. Hypocalcemia is caused by the inability to maintain appropriate circulating calcium concentrations in blood as a consequence of the abrupt demand of calcium by the mammary gland during transition from pregnancy to lactation. Hypocalcemia is known to affect many intracellular functions (Martinez et al., 2012) and to increase the risk of numerous production-related diseases in transition cows, compromising not only animal welfare but also performance. Calcium is required for muscle contraction, and therefore inappropriate concentrations affect the function and motility of the rumen, abomasum, intestine, and uterus (Cameron et al., 1998; Kimura et al., 2006; Goff, 2008), with severe consequences on energy metabolism. Prevention of HC in dairy cows is based either on the administration of calcium (Goff, 2008; Gelfert et al., 2010) or on the prepartum inclusion of diets with a high content of anionic salts, such as chloride or sulfate salts (Charbonneau et al., 2006). These salts reduce the dietary cation-to-anion ratio with the aim of decreasing blood pH, which is compensated in part by bones accepting hydrogen

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ions in exchange for calcium (Lemann et al., 2003). However, the dosage of calcium that needs to be administered to prevent HC differs between cows and depends on factors such as age or previous HC problems. As a limitation, the very low palatability of anionic salts can cause a reduction of feed intake (Moore et al., 2000), which is already low during the last 3 wk before parturition. This reduction in the feed intake increases the risk of various production-related diseases such as mastitis due to impaired immune function (Compton et al., 2007). Therefore, the development of more efficient approaches to avoid HC without the aforementioned negative side-effects is necessary.

Serotonin (5-hydroxytryptamine; **5-HT**), a biogenic amine and tryptophan derivative, is synthesized in the central nervous system, regulating physiological processes related to mood or appetite, and in many peripheral tissues, including the mammary gland. Serotonin has been demonstrated to regulate mammary gland metabolism, including the regulation of calcium concentration in blood transferred from bone (Hernandez et al., 2008, 2007, 2012,). In addition, 5-HT has been also suggested to regulate energy balance, mainly through the modulation of glucose and lipid metabolism (Sugimoto et al., 1990; Watanabe et al., 2014; Laporta et al., 2015). Thus, the presence of 5-HT receptors in several immune cells and the ability of these cells to take up 5-HT suggest that 5-HT influences the activity of the innate and adaptive immune system (Ahern, 2011; Baganz and Blakely, 2013). As it has been described by Hernández-Castellano et al. (2014), the immune status can influence the transfer of immune components from blood to colostrum. As a consequence, it can be hypothesized that 5-HT may also affect IgG concentrations in colostrum. Based on the known actions of 5-HT, we tested the hypothesis that administration of 5-hydroxy-L-tryptophan (**5-HTP**), a 5-HT precursor, causes elevated serum 5-HT concentrations and, in turn, increases calcium concentrations, thus reducing the incidence of HC in cows around parturition (±3 d relative to parturition).

MATERIALS AND METHODS

This study was approved by the Cantonal Committee of Animal Experiments (Canton of Fribourg, Switzerland) and all experimental procedures followed the Swiss law of animal protection. Animal health status was monitored (for diarrhea, mastitis, and fever) and animals did not experience any symptoms of illness apart from those expected in this study (those related to HC such as paresis and fine tremors over the flanks and triceps). At parturition, all cows had an optimal BCS (ranged from 3.0 to 3.5).

Animals and Treatments

Twenty multiparous Holstein dairy cows from the Agroscope research station (Posieux, Switzerland) were randomly assigned to 2 experimental groups of 10 animals each [control (**C**) group and 5-HTP group). On the day before the start of infusions, cows were fitted with indwelling intravenous catheters (Abbocath-T; Hospira Deutschland GmbH, Munich, Germany) with a length of 14 cm and a diameter of 14 gauge in the jugular vein. Both groups received a daily i.v. infusion of 1 L of either 0.9% NaCl (C group) or 0.9% NaCl containing 1 mg of 5-HTP/kg of BW (5-HTP group). According to Laporta et al. (2015), this 5-HTP dosage increased blood 5-HT concentration in late-lactation cows. Infusions lasted for 1 h (0700–0800 h) and were performed from d −10 before the predicted parturition until parturition. Blood samples were collected every morning before the infusions before calving and daily after parturition until d 7. An additional sample was collected on d 30 postpartum. Milk yield of all individual morning and evening milkings was recorded until d 30 postpartum. During the experimental period cows received hay ad libitum (DM content = 890 g/kg of fresh matter, on s 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 concentrate supplementation (consisting of wheat bran, apple pomace, oats, magnesium oxide, molasses, and a vitamin-mineral premix) to meet their energy and nutrient requirements according to the guidelines published by Agroscope (2015). Briefly, cows received and consumed a concentrate (6 MJ of NE_L/kg of DM and 5 g of calcium/kg) before and after parturition (0.5 and 2.5 kg/d and cow, respectively). In addition, cows were supplemented with a vitamin-mineral premix providing 2.5 g of calcium/d before parturition and 31.8 g of calcium/d after parturition.

Sample Collection

Blood samples were taken from the jugular catheter and placed into tubes for plasma collection, containing 3K-EDTA, as well as tubes for serum collection. Blood was stored on wet ice 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 analysis. Milk samples were aliquoted and then stored at −80°C.

Variables Measured in Plasma and Serum

Glucose, fatty acid, and BHB plasma concentrations were measured using commercial kits from Randox (GL364, FA115, and RB1007, respectively; Randox