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The dopamine antagonist domperidone increases prolactin concentration and enhances milk production in dairy cows

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ABSTRACT

In previous studies, our team showed that the inhibition of prolactin (PRL) secretion by the dopamine agonist quinagolide reduces milk production in dairy cows. The objective of this study was to determine the effects of administration of a dopamine antagonist on basal and milking-induced PRL concentrations in blood and on milk production during positive energy balance and feed restriction in dairy cows. Eighteen mid-lactation Holstein cows received daily s.c. injections of either domperidone (300 mg, DOMP, n = 9) or the vehicle, canola oil (CTL, n = 9), for 5 wk. During wk 5, all cows were fed at 65% of their dry matter intake in the previous week. Blood and milk samples were collected before (for blood) and during (for milk) the a.m. milking thrice weekly from d −9 to 41 (8 d after the last injection). In addition, blood samples were collected during the a.m. milking on d −1 (before the first injection), and on d 1, 28, and 34. Basal PRL concentration was similar in both groups before the start of the treatments. Domperidone injections caused a gradual increase in basal PRL concentration. Feed restriction reduced basal PRL concentration in both the CTL and DOMP cows, but PRL concentration remained higher in the DOMP cows. Prolactin concentration remained elevated in the DOMP cows 7 d after the last injection. The milk concentration of PRL increased during the DOMP treatment, but the increase was smaller than that observed in serum. In the CTL cows, the milking-induced PRL release above the premilking concentration was similar on d −1, 1, and 28 but was reduced during feed restriction. In the DOMP cows, the milking-induced PRL release was similar on d −1 and 1 but was reduced on d 28 and 34. Milk production was similar for both groups before the treatments started but was greater in the DOMP cows during the treatment period, at 2.9 ± 0.6 and 2.4 ± 0.6 kg/d greater during wk 3 and 4 of treatment, respectively. Milk production declined in both groups during feed restriction but remained higher in the DOMP cows. Milk production became similar again for both groups after the last injection. In addition, dry matter intake was increased by DOMP. These results support the hypothesis that PRL is galactopoietic in dairy cattle.
Key words: prolactin, feed restriction, lactation persistency, galactopoiesis

INTRODUCTION

Prolactin (**PRL**), as its name implies, is the most important hormone for the control of lactation. In most mammals, the suppression of PRL with bromocriptine strongly inhibits lactation (Taylor and Peaker, 1975; Flint and Gardner, 1994). Although the involvement of PRL in the control of ruminant lactation has been controversial, our team recently demonstrated that the administration of quinagolide, a more specific and more potent PRL-release inhibitor than bromocriptine, decreased milk production in dairy cows (Lacasse et al., 2011; Ollier et al., 2013, 2014, 2015) and that PRL injection attenuated the inhibitor effect (Lacasse et al., 2012). In those studies, even though the basal level of PRL was not clearly associated with the level of milk production, the milking-induced PRL release was correlated with the level of milk production in both PRL-inhibited and control cows. Interestingly, our team observed that feed restriction depresses blood PRL concentration (Ollier et al., 2014, 2015), which suggests that feed restriction may affect the mammary gland by modifying PRL concentration. Further evidence of the galactopoietic action of PRL is provided by the finding that a long-day photoperiod increased PRL concentration and milk production (Bilodeau et al., 1989). Nevertheless, a complete demonstration of the galactopoietic function of PRL requires showing that pharmacologically enhanced PRL concentration has a positive effect on lactation.

The main physiological control of PRL secretion is exerted by the inhibitory action of dopamine on the lactotrophs of the anterior pituitary via dopamine

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D2 receptors (Torre and Falorni, 2007). Dopamine is secreted in the hypothalamus through the tuberoinfundibular dopamine pathway and reaches the pituitary through a portal vascular system. It has been proposed that suckling reduces the activity of the neurons in the tuberoinfundibular dopamine pathway, enabling the release of PRL into the bloodstream (Li et al., 1999). Domperidone (**DOMP**) is a dopamine antagonist that has been shown to induce PRL secretion in several species, including rat (Kato et al., 1980), human (Fujino et al., 1980), and sheep (Deaver et al., 1987). The oral administration of DOMP has been shown to enhance milk production in women (da Silva et al., 2001) and mares (Cross et al., 2012). Therefore, the objective of this study was to determine the effect of DOMP injections on PRL secretion and milk production during positive energy balance and feed restriction in dairy cows.

MATERIALS AND METHODS

Animals and Experimental Design

The experiment was conducted in accordance with the guidelines of the Canadian Council on Animal Care (1993). Eighteen Holstein cows (187 ± 13 DIM) were housed in a tiestall barn at Agriculture and Agri-Food Canada's Dairy and Swine Research and Development Centre (Sherbrooke, QC, Canada). The cows received daily (at 1030 h) s.c. injections of either domperidone (DOMP, n = 9) or the vehicle, canola oil (control, **CTL**, n = 9), for 5 wk. Domperidone (300 mg, Equi-Tox Inc., Central, SC) was injected as an oil suspension in 10 mL of canola oil. During wk 5, all cows were fed at 65% of their DMI in the previous week. The cows were milked twice daily, at 0800 and 2000 h, and milk yield was recorded at each milking. The animals were fed a TMR containing (on a DM basis) 34% corn silage, 21% grass silage, 17.2% corn grain, 15.6% soybean meal, 4.5% chopped dry hay, 3.6% beet pulp, 1.8% nonmineral supplement, 1.7% mineral supplement, and 0.5% calcium carbonate. Feed intake was recorded daily. The BW of each animal was determined at the start and at the end of the experiment.

Caudal blood samples were collected before the a.m. milking 3 d/wk from d −9 to 41 (8 d after the last injection) using uncoated Vacutainer tubes (Becton, Dickinson and Co., Rutherford, NJ). On d −1 (before the start of the treatments), and d 1, 28, and 34, samples were collected from 6 cows per treatment in tubes without additives before, during, and after the a.m. milking (−20, −10, 0, 3, 5, 7, 10, 15, 20, 25, 30, 40, and 60 min relative to the start of milking) from a Silastic catheter (i.d. 1.02 mm, o.d. 2.16 mm; Dow Corning Corp., Midland, MI) inserted into the jugular vein. The blood tubes were left for approximately 2 h at room temperature for clotting before centrifugation (1,900 × *g*, 4°C, 15 min). Serum samples were then kept at −20°C until determination of PRL and NEFA concentrations.

Milk samples were collected at the a.m. milking 3 d/wk from d −9 to 41. Milk lactose, protein, and fat concentrations and SCC were determined in a commercial laboratory (Valacta Inc., Ste-Anne-de-Bellevue, QC, Canada). In addition, aliquots of the milk samples were skimmed by centrifugation (1,900 × *g*, 4°C, 15 min) and stored at −20°C until determination of PRL concentration.

PRL and Metabolite Concentrations

Serum and milk PRL concentrations were measured by RIA as described by Bernier-Dodier et al. (2011). Bovine PRL, rabbit antiserum specific for bovine PRL, and goat anti-rabbit gamma globulin were purchased from the National Hormone and Peptide Program (Harbor-UCLA Medical Center, Torrance, CA). Serum concentration of NEFA was determined using NEFA-HR(2) reagents (Wako Diagnostics, Richmond, VA) as described by Ollier et al. (2014).

Statistical Analysis

Data were analyzed by ANOVA using the MIXED procedure of the SAS software package (SAS Institute Inc., Cary, NC). Time was used as a repeated effect, and animal was used as the subject. Data were analyzed separately for the pretreatment period (d <1), each week of the treatment period (d 1 to 28), the feed-restriction period (d 29 to 35), and the posttreatment period (d >35). Means of the data from the pretreatment period were used as covariates. The amount of PRL released into the blood during milking was calculated by determining the area under the curve between 0 and 40 min relative to the start of milking, and basal PRL concentration was calculated by averaging the concentrations obtained between −20 and 0 min. The proportion of steady-state PRL secreted via milk, which equals the amount of PRL secreted via milk in 24 h multiplied by 100 and divided by the amount of PRL present in the circulation, was calculated according to Singh et al. (2014). Differences were considered statistically significant when $P < 0.05$ and considered a trend when $P < 0.15$.

RESULTS

Serum PRL concentration was not different for both groups of cows before the treatments began ($P > 0.8$;