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Feeding an enhanced diet to Holstein heifers during the preweaning period alters steroid receptor expression and increases cellular proliferation

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ABSTRACT

Preweaning diet and estradiol treatment alters mammary development. Our objectives were to study the effects of diet and estradiol on proliferation of mammary epithelial cells and expression of estrogen receptor α (ESR1) and progesterone receptors (PGR) in these cells. Thirty-six Holstein heifer calves were raised on (1) a control milk replacer fed at 0.44 kg of powder/head per day, dry matter (DM) basis (restricted, R; 20.9% crude protein, 19.8% fat, DM basis), or (2) an enhanced milk replacer fed at 1.08 kg of powder/head per day, DM basis (Enhanced, EH; 28.9% crude protein, 26.2% fat, DM basis). Milk replacer was fed for 8 wk. At weaning, a subset ($n = 6$ /diet) of calves were euthanized and had tissue harvested. Remaining calves received estradiol implants (E_2) or placebo and were euthanized at wk 10 to harvest tissue. Treatments were (1) R, (2) R + E_2 (R- E_2), (3) EH, and (4) EH + E_2 (EH- E_2). One day before euthanasia calves were given bromo-2'-deoxyuridine (BrdU; 5 mg/kg of body weight). At euthanization, mammary parenchyma was removed and fixed. Tissue sections from zone 1 (cisternal), 2 (medial), and 3 (distal) within the mammary gland were stained with hematoxylin and eosin and antibodies to measure expression of ESR1, PGR, and incorporation of BrdU. At wk 8, R-fed calves had more PGR-expressing cells in distal parenchyma; however, PGR expression intensity was greater in EH-fed calves. The proportion of cells expressing ESR1 was not affected by diet, but expression intensity (receptors per positive cell) was greater in EH-fed calves across all zones (62–81%). Overall, the percent BrdU-positive epithelial cells was 2 and 0.5 fold greater for EH-fed calves in zone 2 and 3. The proportion of labeled cells was greater in terminal ductal units than in subtending ducts, and treatment effects were more evident in

terminal ductal units. At wk 10, calves treated with estradiol had 3.9-fold greater PGR expression intensity. The intensity and percent of cells expressing ESR1 was lowest in estradiol-treated calves. Overall, estradiol-treated calves had the greatest number of proliferating epithelial cells. Moreover, in zone 3, EH- E_2 calves had a higher percentage of proliferating cells than in all other treatments. Results indicate both diet and estradiol administration alter proliferation rates of the mammary epithelium and that changes in expression of ESR1 and PGR are involved in enhanced mammary development. The data support our hypothesis that enhanced preweaning feeding increases the mammary tissue responsiveness to mammogenic stimulation.

Key words: mammary gland, calf, estrogen receptor, progesterone receptor

INTRODUCTION

The goal of the replacement heifer industry is to provide the lactating herd with the most profitable animal possible. With replacement rearing accounting for the second largest on-farm expense (Heinrichs, 1993), the need to develop replacement heifers more efficiently is evident.

Much work in the past 2 decades has assessed management of replacement heifers and how these feeding, housing, and care decisions influence the quality of the replacements. However, the area of most emphasis has been nutritional management of the dairy heifer. For some time, a major goal of the replacement industry was to shorten the time needed to transition replacement heifers into the lactating herd. For this to occur, heifer calves must give birth earlier and, in turn, reach puberty and be bred at an earlier age. Because puberty is highly correlated with BW (Sejrsen, 1994), changes in feeding schemes can produce heifers that reach puberty at earlier ages; this requires feeding a diet that encourages greater prepubertal BW gain. Unfortunately, greater prepubertal gains can decrease first-lactation performance by 15% or more (Radcliff et al., 2000), a number that is considered debatable but for which supporting data does exist (Van Amburgh

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et al., 1998). Therefore, it appears uneconomical to encourage greater BW gain at this time.

However, results from recent research trials suggest that not all portions of the prepubertal period are equal with respect to negative effects. In fact, multiple studies suggest that increased BW gain in replacement heifers during the milk-fed (preweaning) stage is beneficial to health and future performance (Drackley et al., 2007; Soberon et al., 2012). Although many studies indicate that a greater rate of gain during the milk-fed stage of life increases first-lactation milk yield, the mechanisms at play remain largely unknown (Khan et al., 2011).

Meyer et al. (2006a) found that by feeding a higher plane of nutrition early in life, mammary fat pad weights and DNA content of the mammary parenchyma (PAR) increased. In their study, however, differences in PAR disappeared when adjusted for BW. Additionally, Brown et al. (2005) found that providing a higher plane of nutrition to calves in early life resulted in more total PAR tissue, PAR DNA, PAR RNA, and concentrations of DNA and RNA in the mammary gland.

In recent reports (Geiger et al., 2016a) we replicated previous work and showed that a much larger heifer with an increased plane of nutrition (i.e., roughly 20 kg heavier at weaning) can be attained by feeding 2 distinctly different planes of nutrition during the preweaning phase of life. Moreover, mammary PAR mass was increased 7.3 fold with enhanced preweaning feeding, mammary tissues from enhanced-fed calves were also more responsive to estrogen stimulation, and the biochemical composition of the PAR and mammary fat pad was normal (Geiger et al., 2016b).

The objective of the current study was to assess the effects of 2 different preweaning diets on expression of receptors for mammogenic steroid hormones and the corresponding effects on the proliferation of mammary epithelial cells within the developing mammary gland. A secondary objective was to assess the effect of exogenous estradiol on tissue development, cell proliferation, and expression of the same parameters when exogenous estradiol was provided to these 2 different groups of calves immediately postweaning. It was our hypothesis that providing a greater plane of nutrition preweaning alters expression of estrogen receptor α (ESR1) and progesterone receptor (PGR) in the population of mammary epithelial cells, and that these changes correspond with changes in cellular proliferation within the developing mammary gland. We further hypothesized that calves fed a higher plane of nutrition and given estradiol immediately postweaning would exhibit the greatest rate of cellular proliferation compared with all other treatments. This would support the idea that better nutrition in early life better prepares the mammary gland to respond to mammogenic stimuli.

MATERIALS AND METHODS

This experiment was conducted under the review and approval of the Virginia Polytechnic Institute and State University Institutional Animal Care and Use Committee (#14-045-DASC).

Animal Handling and Experimental Design

The experimental design and animal handling were as previously described (Geiger et al., 2016a). Briefly, Holstein, heifer calves (initial BW = 39.0 ± 4.4 kg; initial age = 6.0 ± 2.0 d) were assigned to 1 of 2 experimental milk replacers (MR; n = 18/MR): (1) a restricted MR (20.9% CP, 19.8% fat, DM basis; Southern States Cooperative Inc., Richmond, VA) fed at 0.44 kg/head per day, DM basis; or (2) an enhanced MR (28.9% CP, 26.2% fat, DM basis; Land O'Lakes Animal Milk Products Co., Shoreview, MN) fed at 1.08 kg/head per day, DM basis. Starter (25.6% CP, 4.0% fat, DM basis; Southern States Cooperative Inc.) was offered at the end of wk 4 of the trial. A subset of calves (n = 6/diet) were euthanized upon weaning, which occurred at wk 8, to assess dietary effects on mammary gland development. The remaining calves (n = 24) were either given an estradiol (E₂) implant (Compudose, Elanco Animal Health, Greenfield, IN) or a placebo implant at weaning. This produced treatment groups (n = 6/treatment) of (1) calves restricted-fed and given a placebo implant (R), (2) calves restricted-fed and given an E₂ implant (R-E₂), (3) enhanced-fed calves given a placebo implant (EH), and (4) enhanced-fed given an E₂ implant (EH-E₂). After 2 wk of E₂ or placebo treatment, all remaining animals were euthanized and mammary tissue was harvested to assess the effect of E₂ on calves fed the 2 different diets. This euthanasia and harvest occurred at wk 10 and calves were given i.v. injections of bromo-2'-deoxyuridine (BrdU) at a dose of 5 mg/kg, 24 h before sampling.

Mammary Tissue Collection and Sample Preparation

Animal euthanasia and sample preparation are outlined in detail in a previous work (Geiger et al., 2016a,b). The right fore quarter of the udder was used to collect tissue samples that were fixed for immunohistochemistry. Briefly, the dissected parenchymal mass with the teat attached was partially bisected or butterflied (depending on size) and immersed in a container of fixative, as described in a previous study (Tucker et al., 2016). Examples of dissected, fixed tissues are shown in Geiger et al. (2016a). After fixation, these tissues were subsampled to provide PAR from near the teat (zone 1), midway (zone 2) to the outer region

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