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Prepartum 2,4-Thiazolidinedione Alters Metabolic Dynamics and Dry Matter Intake of Dairy Cows

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ABSTRACT

Thiazolidinediones (TZD) are potent, synthetic ligands for peroxisome proliferator activated receptor-gamma (PPAR-γ) that reduce plasma nonesterified fatty acids (NEFA) and potentiate the action of insulin in peripheral tissues of several species. Holstein cows (n = 9) entering their second or greater lactation were used to determine whether late prepartum administration of TZD would affect periparturient metabolism and milk production. Cows were limit-fed a total mixed ration (TMR) during the prepartum period to provide no more than 130% of predicted energy requirements. During the postpartum period cows were fed a common TMR for ad libitum intake. Cows were administered either 2,4-TZD (4.0 mg/kg of body weight) or saline (control) by intrajugular infusion once daily from 25 d before expected parturition until parturition. Plasma samples were collected daily from 26 d before expected parturition through 7 d postpartum. Plasma NEFA concentrations decreased during the prepartum period (d −21 to −1; 70 vs. 83 ± 4 μEq/L) and tended to be decreased during the peripartum period (d −7 to d +7; 113 vs. 205 ± 32 μEq/L) due to prepartum TZD administration. Plasma concentrations of glucose were not affected by treatment; however, plasma β-hydroxybutyrate concentrations decreased in TZD-treated cows (8.6 vs. 10.7 ± 1.7 mg/dL) as parturition approached, and plasma insulin concentrations increased during the peripartum period (0.65 vs. 0.38 ± 0.07 ng/mL). Postpartum liver triglyceride and glycogen content was not affected by treatment. Prepartum TZD administration tended to increase dry matter intake during the peripartum and postpartum periods (16.6 vs. 14.6 ± 0.8 kg/d and 20.0 vs. 17.2 ± 1.2 kg/d, respectively). Milk yield for the first 30 d postpartum and milk composition measured on d 8 postpartum were not affected by treatment. There was no effect of prepartum TZD administration on insulin-dependent glucose utilization assessed using insulin challenge during either the prepartum or postpartum periods. These results suggest that administration of TZD during the late prepartum period has the potential to improve metabolic health and DMI of periparturient dairy cows and warrants further investigation.
Key words: transition cow, thiazolidinedione, peroxisome proliferator activated receptor-gamma

INTRODUCTION

Periparturient dairy cows undergo tremendous adaptations in energy metabolism, particularly in glucose and lipid metabolism, as they transition from late pregnancy to early lactation (Bell, 1995). The homeorhetic coordination required to actualize these metabolic adaptations to support lactation involves a variety of processes and a number of different tissues in the body (Bauman and Elliot, 1983; Bell, 1995). Overall performance and well-being of early lactation cows depends upon the successful coordination of metabolism in support of these adaptations.

One of the key targets for research in transition cow metabolism (Overton and Waldron, 2004) has been aspects of lipid metabolism that relate to mobilization of NEFA from adipose reserves and subsequent metabolism by the liver. Hepatic uptake of NEFA in excess of oxidation or export leads to accumulation of triglycerides in the liver, which increases the risk for development of ketosis and associated disorders (Overton and Waldron, 2004). Few published studies have focused on changes in adipose tissue and the potential to modulate metabolism of adipose tissue to moderate the acute spike in circulating NEFA concentrations that occurs at or after parturition.

One of the primary homeorhetic adaptations during the periparturient period involves the development of insulin resistance during late pregnancy in the form of decreased tissue responses to insulin that continue into early lactation (Smith, 2004). Insulin resistance in peripheral tissues facilitates glucose sparing for the mammary gland (Bauman and Elliot, 1983). Mobilization

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of NEFA from adipose tissue is facilitated by insulin resistance. Recent data from our laboratory (Smith, 2004; Smith et al., 2006) suggest that tissue responses to insulin in dairy cows may be less during the late prepartum period than during the immediate postpartum period.

Recent research suggested that overfeeding dairy cows during the prepartum period may accentuate insulin resistance in adipose tissue, leading to increased NEFA mobilization, lower DMI, and greater risk for lipid-related metabolic disorders (Holtenius et al., 2003). Increased circulating NEFA during the immediate peripartum period likely contributes to the depression in DMI experienced during the immediate peripartum period caused by increased hepatic energy status from oxidation of NEFA (Allen et al., 2005); this scenario likely is exacerbated by increased insulin resistance in adipose tissue caused by overfeeding during the prepartum period.

Most aspects of insulin resistance in adipose tissue are likely mediated through the action of peroxisome proliferator activated receptor-gamma (**PPAR-γ**). Peroxisome proliferator activated receptor-gamma belongs to a subfamily of the nuclear-receptor family that regulates gene expression in response to ligand binding (Hammarstedt et al., 2005) and is highly expressed in bovine adipose tissue (Sundvold et al., 1997). Activation of PPAR-γ potentiates adipocyte differentiation, stimulates insulin action, and decreases the release of free fatty acids from the adipocyte (Houseknecht et al., 2002).

There are many natural ligands for PPAR-γ including fatty acids and prostaglandins (Houseknecht et al., 2002); however, the most potent ligands include a family of compounds known as the thiazolidinediones (**TZD**). When administered to animal models of noninsulin-dependent diabetes mellitus, TZD increased insulin action, decreased plasma free fatty acids, and improved pancreatic β-cell function. Limited research has been conducted on the activation of PPAR-γ and the administration of synthetic PPAR-γ ligands, specifically TZD, in ruminants. Kushibiki et al. (2001) determined that administration of TZD to steers injected with tumor necrosis factor-α (**TNF-α**) to induce insulin resistance decreased plasma concentrations of NEFA, insulin, and glucagon, suggesting that administration of TZD restored insulin action by reducing circulating NEFA.

We hypothesized that activation of PPAR-γ through administration of TZD to dairy cows during the prepartum period would modulate specific aspects of insulin resistance in adipose tissue and decrease circulating concentrations of NEFA during the periparturient period, which may alter the dynamics of DMI during the peripartum period. Therefore, the objectives of this experiment were to determine the metabolic effects during the periparturient period of TZD administration during the late prepartum period.

MATERIALS AND METHODS

Animals, Treatments, and Sampling

All procedures involving animals were approved before the onset of the experiment by the Cornell University Institutional Animal Care and Use Committee, and the experiment commenced in September 2005 and ended in January 2006. Holstein cows (n = 14) entering their second or later lactation that had been dried off at 60 d before expected calving were selected from the Cornell Teaching and Research Center dairy herd and moved to individual tie stalls approximately 32 d before expected parturition.

Cows were fitted with an indwelling jugular catheter (MicroRenathane Implantation Tubing, 2.03 mm o.d. × 1.02 mm i.d.; Braintree Scientific Inc., Braintree, MA) on d 27 before expected parturition. Beginning on d 25 before expected parturition, cows (n = 7 per treatment) were assigned to 1 of 2 treatments in a completely randomized design and administered either TZD (4.0 mg/kg of BW) or saline (control) by intrajugular infusion once daily at 1300 h. Daily administration of treatments continued until parturition. The TZD was obtained as 2,4-thiazolidinedione from Sigma Chemical Co. (St. Louis, MO). Cow assignment to treatments was balanced for BCS and calculated previous 305-d mature-equivalent milk yield. Cows were limit-fed a TMR during the prepartum period such that cows would consume no more than 130% of predicted NE_L requirements (NRC, 2001). During the postpartum period cows were fed a lactation TMR for ad libitum intake. Individual DMI was recorded from 32 d before expected parturition through 8 d postpartum. Ingredient and chemical composition of the diets fed during the experiment are described in Table 1. All nonforage ingredients in both prepartum and postpartum diets were blended by a commercial feed mill into separate concentrate mixtures, and diet mixing at the farm consisted of mixing the component forages with the appropriate concentrate mixture. Fresh feed was provided each morning at 1000 h, orts were weighed and recorded daily, and water was made available at all times. Samples of the forages and concentrate mixtures were obtained weekly throughout the experiment, and DM content determined by drying at 55°C until static weight. Amounts of individual feed components in the TMR were adjusted weekly based on changes in the DM content of these feed components. Samples of both the prepartum and postpartum TMR were obtained weekly throughout the