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Hepatic mRNA expression for genes related to somatotropic axis, glucose and lipid metabolisms, and inflammatory response of periparturient dairy cows treated with recombinant bovine somatotropin

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ABSTRACT

Objectives of this experiment were to evaluate the effects of recombinant bovine somatotropin (rbST) treatment of periparturient dairy cows on hepatic mRNA expression for genes related to the somatotropic axis, insulin, glucose, and lipid metabolism, inflammation, and oxidative stress. Holstein cows were enrolled in the experiment at 253 ± 3 d of gestation and assigned to 1 of 3 treatments: untreated control (n = 53), 87.5 mg of rbST (n = 56; rbST87.5), and 125 mg of rbST (n = 57; rbST125). Cows in the rbST87.5 and rbST125 treatments received weekly injections of rbST from −21 to 28 d relative to calving. A subsample of cows (control = 20, rbST87.5 = 20, rbST125 = 20) was randomly selected for collection of liver samples according to expected calving date, BCS, and previous lactation 305-d mature equivalent milk yield. Only cows that had liver sampled at −21 ± 3, −7 ± 3, and 7 ± 3 d relative to calving were used in the current experiment. Blood, sampled weekly from −28 to 21 d relative to calving, was used to determine the concentrations of growth hormone, insulin-like growth factor 1, insulin, cortisol, fatty acids, β-hydroxybutyrate, glucose, haptoglobin, and tumor necrosis factor-α. Liver samples were used to determine hepatic mRNA expression of 50 genes. Treatment with rbST increased growth hormone concentrations during the postpartum period (control = 9.0 ± 0.7, rbST87.5 = 15.3 ± 1.0, rbST125 = 18.5 ± 1.3 ng/mL) and increased insulin-like growth factor 1 concentrations during the prepartum period (control = 107.4 ± 7.2, rbST87.5 = 126.9 ± 6.6, rbST125 = 139.4 ± 6.9 ng/mL). Control cows had greater postpartum concentrations of β-hydroxybutyrate (control = 776.4 ± 64.0, rbST87.5 = 628.4 ± 59.7, rbST125 = 595.4 ± 60.9 μmol/L) than rbST cows. The rbST87.5 and rbST125 treatments upregulated the hepatic mRNA expression for somatotropic axis genes (*GHR*, *GHR1A*, *IGF1*, *IGFBP3*, and *SOCS2*) on d −7 relative to calving and upregulated the mRNA expression for *SOCS2* on d 7. On d −7, rbST87.5 and rbST125 treatments increased mRNA expression for genes involved in hepatic lipid transport (*ANGPTL4*, *APOA5*, *APOB100*, and *SCARB1*) and downregulated mRNA expression for *PPARD*, which is involved in lipid storage. On d 7, rbST tended to upregulate the mRNA expression for genes involved in gluconeogenesis (*PCK1*) and fatty acid β-oxidation (*ACOX1*), and downregulated the mRNA expression for genes involved in inflammation (*TNFRSF1A*, *ICAM1*, *CXCL1*, *MYD88*, *HIF1A*, *IL1RN*, *NFKBIA*, and *SOCS3*) and oxidative stress (*XBP1*). Administration of rbST during the periparturient period may improve liver function and health by increasing hepatic capacity for gluconeogenesis and lipid transport and by reducing inflammation and oxidative stress.

Key words: periparturient cows, recombinant bovine somatotropin, hepatic gene expression

INTRODUCTION

The liver performs essential functions in the body by uniquely expressing genes encoding proteins involved in glucose, lipid, and protein metabolism, ketogenesis, immune function, detoxification, hormone catabolism, vitamin and mineral metabolism, and a variety of other functions (Donkin, 2012). Postpartum cow health is closely associated with the capacity of the liver to cope with the changes in nutrient supply and shifting metabolic demands that accompany the initiation of lactation (Drackley et al., 2001). In periparturient dairy cows, the liver has an important role in metabolic regulation and control of the somatotropic axis to successfully adapt to the negative energy balance (**NEB**; Grummer et al., 2004). During NEB the expression of growth hormone (**GH**) 1-α receptors (**GHR1A**) by

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the liver is downregulated to decrease IGF-1 synthesis and its inhibitory effects on synthesis and secretion of GH (Bauman, 2000). Therefore, GH concentrations are increased in periods of NEB, such as the periparturient period, to favor nutrient partitioning for lactogenesis (Bell and Bauman, 1997). The pivotal role of GH in nutrient partitioning includes major alterations in metabolism of carbohydrates and lipids (Lupu et al., 2001). In adipose tissue, GH acts to facilitate lipolysis, increase insulin resistance to reduce glucose uptake and oxidation, and to decrease lipid synthesis (Boyd and Bauman, 1989). In the liver, GH increases gluconeogenesis (Cohick et al., 1989) through the regulation of enzymes, such as phosphoenolpyruvate carboxykinase (**PCK**), suppression of insulin's inhibitory effect on gluconeogenesis (Velez and Donkin, 2004), and increased hepatic fatty acid oxidation to CO_2 (Pocius and Hertlein, 1986).

From late gestation to early lactation, insulin resistance and GH-induced lipolysis cause a marked increase in fatty acids concentration and influx into the liver, which experiences a pronounced metabolic stress to maintain homeostasis (Drackley et al., 2001). The liver takes up approximately one-third of the whole body fatty acid flux, and this often exceeds its oxidation capacity, increasing the risk of liver lipidosis and ketosis (Drackley et al., 2001). During the peripartum period the liver is exposed to a variety of inflammatory factors, such as LPS, proinflammatory cytokines, and reactive oxygen species. These inflammatory factors are increased during the periparturient period due to alterations in gastrointestinal physiology, associated with changes in feed intake and composition, and episodes of infectious (e.g., metritis and mastitis) and gastrointestinal (e.g., SARA and displacement of the abomasum) diseases (Plaizier et al., 2008; Vels et al., 2009). Consequently, periparturient cows may present inflammation of the liver, which may induce an acute phase response (Vels et al., 2009), metabolic disorders, and unfold protein response to oxidative stress (Gessner et al., 2014) that collectively result in impaired liver function.

Treatment of lactating dairy cows with recombinant bovine somatotropin (**rbST**) increased liver gluconeogenesis, suppressed insulin's inhibitory effect on gluconeogenesis (Peel and Bauman, 1987), and increased complete oxidation of fatty acids in bovine liver slices (Pocius and Hertlein, 1986), which are expected to improve metabolic parameters. Effects of rbST treatment of periparturient cows on metabolic parameters and health are less clear. Whereas treatment of periparturient cows with 500 mg of rbST every 14 d increased glucose concentration, reduced concentrations of fatty acids and BHB, and increased milk yield according to some (Putnam et al., 1999), it reduced FCM yield according to others (Eppard et al., 1996). Reduced doses of rbST (142.8 to 325 mg of rbST every 14 d) given to periparturient cows increased IGF-1, insulin, and glucose concentrations but, again, effects on milk yield and health were diverse (Gulay et al., 2003, 2004, 2007; Gohary et al., 2014). In a recent experiment, periparturient Holstein cows were treated with 0, 87.5, and 125 mg of rbST weekly, and those treated with 125 mg had increased IGF-1 concentrations, improved responses associated with innate and adaptive immunity, and reduced BHB concentrations (Silva et al., 2015). Therefore, treatment of periparturient cows with reduced doses of rbST has the potential to significantly affect liver function.

Enhanced knowledge of the processes that regulate liver function and factors that potentiate the capacity of liver to coordinate shifts in nutrient supply and demand by other tissues may lead to significant improvements in peripartum cow management and health. Therefore, the hypotheses of the current experiment were that weekly administration of rbST to peripartum dairy cows would upregulate hepatic mRNA expression for genes related to the somatotropin axis (e.g., *GHR*, *GHR1A*, *IGF1*, and *INSR*), gluconeogenesis (e.g., *G6PC*, *PC1*, and *PCK1*), lipid oxidation and transport (e.g., *ACOX1*, *APOA5*, *APOB100*, and *SCARB1*), and downregulate the expression of mRNA for genes related to ketogenesis (e.g., *HMGCLL1*), lipid synthesis and accumulation (e.g., *DGAT1* and *PPARD*), inflammation (e.g., *MYD88*, *NFKB1*, *HIF1*, and *CXCL1*), and oxidative stress (e.g., *XBP1*). The objectives of the current experiment were to evaluate the effects of peripartum rbST treatment of dairy cows on hepatic mRNA expression for genes related to the somatotropic axis, glucose and lipid metabolisms, inflammation, and oxidative stress.

MATERIALS AND METHODS

Animals, Enrollment, and Treatments

All animal procedures conducted during this experiment were approved by the Institutional Animal Care and Use Committee from the University of Minnesota (protocol #1306–30734A). Cows used in the current experiment are a subgroup of cows used in an experiment that evaluated the effects of rbST treatment during the periparturient period on immune parameters (Silva et al., 2015). Detailed information regarding facilities, management, and nutrition has been previously described (Silva et al., 2015).

Multiparous Holstein cows (lactation = 1 to 6) from a commercial freestall herd located in northwest Wisconsin, with BCS 3.75 to 4.75 (Ferguson et al., 1994) and