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Hepatic gene expression involved in glucose and lipid metabolism in transition cows: Effects of fat mobilization during early lactation in relation to milk performance and metabolic changes

C. Weber,* C. Hametner,* A. Tuchscherer,* B. Losand,† E. Kanitz,* W. Otten,* H. Sauerwein,‡ R. M. Bruckmaier,§ F. Becker,* W. Kanitz,* and H. M. Hammon*[1]
*Leibniz Institute for Farm Animal Biology (FBN), 18196 Dummerstorf, Germany
†State Institute of Animal Production, 18196 Dummerstorf, Germany
‡Institute of Animal Science, Physiology & Hygiene Unit, University of Bonn, 53115 Bonn, Germany
§Veterinary Physiology, Vetsuisse Faculty, University of Bern, 3001 Bern, Switzerland

ABSTRACT

Insufficient feed intake during early lactation results in elevated body fat mobilization to meet energy demands for milk production. Hepatic energy metabolism is involved by increasing endogenous glucose production and hepatic glucose output for milk synthesis and by adaptation of postcalving fuel oxidation. Given that cows differ in their degree of fat mobilization around parturition, indicated by variable total liver fat concentration (LFC), the study investigated the influence of peripartum fat mobilization on hepatic gene expression involved in gluconeogenesis, fatty acid oxidation, ketogenesis, and cholesterol synthesis, as well as transcriptional factors referring to energy metabolism. German Holstein cows were grouped according to mean total LFC on d 1, 14, and 28 after parturition as low [<200 mg of total fat/g of dry matter (DM); n = 10], medium (200–300 mg of total fat/g of DM; n = 10), and high (>300 mg of total fat/g of DM; n = 7), indicating fat mobilization during early lactation. Cows were fed total mixed rations ad libitum and held under equal conditions. Liver biopsies were taken at d 56 and 15 before and d 1, 14, 28, and 49 after parturition to measure mRNA abundances of pyruvate carboxylase (*PC*); phosphoenolpyruvate carboxykinase; glucose-6-phosphatase; propionyl-coenzyme A (CoA) carboxylase α; carnitine palmitoyl-transferase 1A (*CPT1A*); acyl-CoA synthetase, long chain 1 (*ASCL1*); acyl-CoA dehydrogenase, very long chain; 3-hydroxy-3-methylglutaryl-CoA synthase 1 and 2; sterol regulatory element-binding factor 1; and peroxisome proliferator-activated factor α. Total LFC postpartum differed greatly among cows, and the mRNA abundance of most enzymes and transcription factors changed with time during the experimental period. Abundance of *PC* mRNA increased at parturition to a greater extent in high- and medium-LFC groups than in the low-LFC group. Significant LFC × time interactions for *ACSL1* and *CPT1A* during the experimental period indicated variable gene expression depending on LFC after parturition. Correlations between hepatic gene expression and performance data and plasma concentrations of metabolites and hormones showed time-specific relations during the transition period. Elevated body fat mobilization during early lactation affected gene expression involved in gluconeogenesis to a greater extent than gene expression involved in lipid metabolism, indicating the dependence of hepatic glucose metabolism on hepatic lipid status and fat mobilization during early lactation.
Key words: dairy cow, fat mobilization, hepatic energy metabolism, gene expression

INTRODUCTION

The transition from gestation to lactation involves distinctive changes in carbohydrate and lipid metabolism in dairy cows, due to the fact that the energy demand for milk production increases largely after parturition, and nutrient intake during early lactation is not capable to meet energy requirements (Ingvartsen and Andersen, 2000; Drackley et al., 2001). During this time, dairy cows undergo a period of negative energy balance (**NEB**) that is characterized by the mobilization of body reserves of different tissues, in particular adipose tissue, even when voluntary feed intake increases. In this regard, lipid mobilization in early lactation is considered as noncompromised and varies largely among cows (Ingvartsen et al., 2003). When blood NEFA concentrations increase, NEFA will be taken up by the liver gradually and will be either completely oxidized to carbon dioxide, incompletely oxidized to ketone bodies, or reesterified and stored as triacylglycerides (Herdt, 2000; Drackley et al., 2001; Bobe et al., 2004). Severe NEB linked with excessive fat

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[1]Corresponding author: hammon@fbn-dummerstorf.de

mobilization and fatty liver may lead to metabolic related diseases, such as ketosis and fatty liver disease in dairy cows (Goff and Horst, 1997; Herdt, 2000; Geelen and Wensing, 2006). Prior investigations established huge variations among dairy cows in coping with these metabolic challenges during the transition from pregnancy to lactation. Consequently, some cows are able to adapt very well to new metabolic requirements in early lactation, whereas others do not (Goff and Horst, 1997; Herdt, 2000). The processes of metabolic adaptation depend also on individual cow factors and not only on environmental and management conditions (Jorritsma et al., 2003; Hammon et al., 2009; van Dorland et al., 2009).

The investigation of factors that can predict the metabolic status of dairy cows and the potential susceptibility for periparturient disorders is the focus of many studies and gains on importance in dairy cattle management. We have recently established that liver fat concentration (**LFC**) after parturition is an indicator for fat mobilization during the transition period and, therefore, a useful marker for the metabolic load in dairy cows during this time (Hammon et al., 2009; Weber et al., 2013). In addition, huge variation was observed among cows with same level of milk production concerning the degree of fat mobilization and the degree of fat mobilization was related to DMI, NEB, and plasma concentrations of glucose, NEFA, and BHBA (Hammon et al., 2009; Weber et al., 2013). These findings suggest different metabolic strategies among cows to support energy demands for milk synthesis during early lactation.

Due to the elevated glucose demand for milk synthesis at the beginning of lactation, the liver increases glucose production, and hepatic glucose output markedly increases to cover glucose demands of the mammary gland (Drackley et al., 2001; Reynolds et al., 2003; Aschenbach et al., 2010). Because of the elevated glucose demands and the insufficient energy intake during early lactation, metabolic and endocrine changes support adaptation of hepatic energy metabolism at the beginning of lactation by stimulating gene expression of transcription factors and enzymes involved in glucose production, FA oxidation, and ketogenesis in the liver (Greenfield et al., 2000; Loor et al., 2005; Loor, 2010). The expression of genes involved in hepatic energy metabolism are affected by diet and nutrient intake (Velez and Donkin, 2005; Loor et al., 2006), but also vary among cows with different metabolic types (Hammon et al., 2010) or variation in postcalving energy mobilization (van Dorland et al., 2009; Hammon et al., 2009). Therefore, changes in LFC, which mirror variations in body fat mobilization and energy metabolism after parturition, may affect hepatic gene expression of key enzymes involved in gluconeogenesis, FA oxidation, and ketogenesis of dairy cows.

The objective of the present study was to determine differences in hepatic gene expression of key enzymes and transcription factors involved in carbohydrate and lipid metabolism in high-yielding dairy cows that vary in fat mobilization during the transition period and to relate time changes of hepatic gene expression data to performance and metabolic data that were published recently (Weber et al., 2013). We hypothesized that gene expression with regard to hepatic carbohydrate and lipid metabolism may be impaired in cows with elevated hepatic fat accumulation. Our findings may contribute to the understanding of hepatic energy metabolism around parturition that relates to differing fat mobilization, which may help to identify strategies for metabolic adaptation of the liver during the transition from pregnancy to lactation.

MATERIALS AND METHODS

Animals, Husbandry, Feeding, and Milking

The experimental procedures were carried out according to the animal care guidelines and were approved by the relevant authorities of the State Mecklenburg-Vorpommern, Germany (LALLF M-V TSD 7721.3-1.1-005/09). German Holstein cows (n = 27), with comparable milk production (second lactation >10,500 kg of milk in 305 d), were purchased from 4 local farms after about 300 DIM in second lactation. Cows were studied from wk 8 before parturition to 49 DIM in their third lactation. The drying off period started at wk 8 before expected parturition and cows received dry period therapy (Nafpenzal; Intervet Deutschland GmbH, Unterschleißheim, Germany). Cows were then kept in a freestall barn of the Leibniz Institute for Farm Animal Biology (FBN; Dummerstorf, Germany) to adapt to the new environmental conditions. Housing and feeding management was the same for all cows during the experimental period between wk 8 before parturition and 49 DIM. From d 10 before to d 1 after parturition cows were housed in calving boxes. Cows were clinically healthy and did not suffer from production diseases such as ketosis, fatty liver disease, rumen acidosis, milk fever, or displacement of abomasum, or from infectious diseases.

Diets were provided as TMR ad libitum. The TMR was placed in troughs on scales, which were connected to a computer, and individual feed intake was calculated for each day. Diets were fed at 0700 and 1600 h. Cows received separate dry-off (from wk 8 to 4 before calving), close-up (from wk 3 to calving), and lactation diets according to the recommendations of the German