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Prepartal high-energy feeding with grass silage-based diets does not disturb the hepatic adaptation of dairy cows during the periparturient period

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ABSTRACT

The liver of dairy cow naturally undergoes metabolic adaptation during the periparturient period in response to the increasing demand for nutrients. The hepatic adaptation is affected by prepartal energy intake level and is potentially associated with inflammatory responses. To study the changes in the liver function during the periparturient period, 16 cows (body condition score = 3.7 ± 0.3, mean ± standard deviation; parity = second through fourth) were allocated to a grass silage-based controlled-energy diet (104 MJ/d) or a high-energy diet (135 MJ/d) during the last 6 wk before the predicted parturition. Liver samples were collected by biopsy at 8 d before the predicted parturition (−8 d) and at 1 and 9 d after the actual parturition (1 and 9 d). The lipidomic profile of liver samples collected at −8 and 9 d was analyzed using ultra performance liquid chromatography-mass spectrometry–based lipidomics. Liver samples from all the time points were subjected to microarray analysis and the subsequent pathway analysis with Ingenuity Pathway Analysis software (Ingenuity Systems, Mountain View, CA). Prepartal energy intake level affected hepatic gene expression and lipidomic profiles prepartum, whereas little or no effect was observed postpartum. At −8 d, hepatic lipogenesis was promoted by prepartal high-energy feeding through the activation of X receptor/retinoid X receptor pathway and through increased transcription of thyroid hormone-responsive (*THRSP*). Hepatic inflammatory and acute phase responses at −8 d were suppressed (z-score = −2.236) by prepartal high-energy feeding through the increase in the mRNA abundance of suppressor of cytokine signaling 3 (*SOCS3*) and the decrease in the mRNA abundance of interleukin 1 (*IL1*), nuclear factor kappa B 1 (*NFKB1*), apolipoprotein A1 (*APOA1*), serum amyloid A3 (*SAA3*), haptoglobin (*HP*), lipopolysaccharide-binding protein (*LBP*), and inter-α-trypsin inhibitor heavy chain 3 (*ITIH3*). Moreover, prepartal high-energy feeding elevated hepatic concentrations of C18- (7%), C20- (17%), C21- (26%), C23-sphingomyelins (26%), and total saturated sphingomyelin (21%). In addition, cows in both groups displayed increased lipogenesis at the gene expression level after parturition and alterations in the concentration of various sphingolipids between the first and last samplings. In conclusion, prepartal high-energy feeding promoted lipogenesis and suppressed inflammatory and acute phase responses in the liver before parturition, whereas only minor effects were observed after parturition.
Key words: dairy cow, periparturient period, physiological adaptation, microarray, lipidomic profiling

INTRODUCTION

Dairy cows undergo a series of physiological adaptations during the periparturient period due to the increasing energy requirement and the subsequent negative energy balance. The physiological adaptations are partly mediated by insulin resistance (**IR**) and the change in plasma insulin concentration (Bell and Bauman, 1997). These changes lead to the mobilization of body reserves to the tissues in demand (Bell, 1995; Vernon, 2005). Part of the mobilized nutrients are allocated to the liver, where they induce hepatic adaptation, including increased gluconeogenesis and ketogenesis (Aiello et al., 1984; Herdt, 2000). Hepatic adaptation is regulated at gene expression level, as altered mRNA abundance near calving was observed in genes involved in various metabolic pathways (Loor et al., 2005; McCarthy et al., 2010). In addition, hepatic adaptation is potentially associated with the inflammatory status, as negative energy balance is accompanied by increased inflammation induced by proinflammatory cytokines (Trevisi et al., 2012), which stimulate hepatic

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synthesis and secretion of positive acute phase proteins (Bionaz et al., 2007).

Hepatic adaptation is potentially affected by prepartal energy intake level of cows. Prepartal high-energy feeding has been reported to exacerbate the lipid mobilization from adipose tissue (**AT**), particularly after parturition, as characterized by the elevated plasma nonesterified fatty acid (**NEFA**) level (Douglas et al., 2006; Janovick et al., 2011), and evidenced by the decreased expression of lipogenic genes in AT (Selim et al., 2015). As a consequence, the liver may be supplied with the excessive abundance of NEFA, which promotes hepatic lipogenesis and may lead to various metabolic disorders (Ingvartsen, 2006; Loor et al., 2006). Moreover, excessive energy intake prepartum and increased visceral adiposity may predispose dairy cows to inflammation and impaired liver function (Loor et al., 2006). In humans and mice, inflammation is considered as a mechanism that induces IR (McArdle et al., 2013). However, there are contradicting reports whether prepartal high-energy feeding (Mann et al., 2016; Salin et al., 2017) or increased adiposity (Shahzad et al., 2014; De Koster et al., 2015) leads to increased systemic IR in periparturient cows.

Sphingolipids are a class of lipids closely associated with the glucose homeostasis in human and mice (Larsen and Tennagels, 2014). Ceramides (**Cer**), the most abundant sphingolipids in the cell, have been recognized to trigger IR, and their production is influenced by the inflammatory response (Chavez and Summers, 2012). In recent years, the application of lipidomics has enabled novel insights into the role of sphingolipids in the physiological adaptation in periparturient cows. Changed sphingolipid concentrations near calving were reported in the plasma, liver, AT, and skeletal muscle of cows (Imhasly et al., 2015; Qin et al., 2017; Rico et al., 2017). Comparisons between cows of different adiposity further suggested the associations between lipid mobilization and the concentrations of Cer, hexosyl ceramide (**HexCer**), and lactosylceramide in plasma and liver and the association between systemic IR and specific Cer during the periparturient period (Rico et al., 2015, 2017). Moreover, prepartal high-energy feeding was reported to increase the concentration of specific Cer and the total concentration of sphingomyelin (**SM**) in AT near calving (Qin et al., 2017).

We aimed to study effects of prepartal energy level on the hepatic adaptation of dairy cows during the periparturient period through the parallel analyses on global gene expression and lipidomic profiles. First, we hypothesized that prepartal high-energy feeding increases hepatic lipogenesis. Second, we hypothesized that prepartal high-energy feeding increases hepatic Cer concentrations and upregulates genes related to inflammation during the periparturient period.

MATERIALS AND METHODS

Animals, Diets, Samplings, and Glucose Tolerance Tests

The feeding experiment, feed composition, and collection of biopsies were described in detail in Selim et al. (2014). Sixteen Finnish Ayrshire dairy cows were involved in the feeding experiment in a randomized complete-block design. The cows were paired according to parity (second through fourth), BW (693 ± 57 kg, mean ± SD), and BCS (3.7 ± 0.3). The 2 cows in each pair were randomly allocated to 2 dietary treatment groups on 44 ± 5 d before the actual parturition date. The grass silage-based dietary treatments included a controlled-energy (**CON**) diet (100% of the energy requirement of pregnant dairy cow; Luke, 2018) and a high-energy (**HE**) diet targeting 150% of the energy requirements of a pregnant cow. In the ad libitum-fed HE group, the actual average energy intake was 144% of the energy requirement of pregnant dairy cow during the first 3 wk of experimental feeding. During the last 3 wk before the predicted parturition, the energy allowance of the HE group decreased by 5% on alternate days by gradually restricting DMI as described in more detail by Salin et al. (2017). The average ME was 99 MJ/d in the CON group and 141 MJ/d in the HE group from wk 6 to 4 prepartum, and 109 MJ/d in the CON group and 128 MJ/d in the HE group from wk 3 to 1 prepartum. After parturition, all cows were fed wilted grass silage ad libitum, supplemented with increasing amount of small grain-based concentrate, starting from 5 kg/d on the day of parturition and increasing to 9 kg/d at 9 d postpartum (average ME was 11 MJ/d during the first 2 wk of lactation). The liver samples were collected by biopsy 8 d before the predicted parturition (11 ± 5 d in the actual operation) and 1 and 9 (±1) d postpartum (the 3 time points are hereafter represented as −8 d, 1 d, and **9 d**). Lipidomic and microarray analyses were conducted on 22 and 32 biopsy samples, respectively. The selection of samples was random with respect to pairs to represent the design of the whole study. Intravenous glucose tolerance tests (**IVGTT**) were performed on the cows 10 ± 5 d before the actual parturition and 10 ± 1 d postpartum, and the results have been published by Salin et al. (2017). The basal NEFA concentrations at 10 ± 5 d before the parturition and 10 ± 1 d postpartum were calculated by averaging the measurements on the blood samples collected 15 and 5 min before the IVGTT (Salin et al., 2017).