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Insulin-dependent glucose metabolism in dairy cows with variable fat mobilization around calving

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ABSTRACT

Dairy cows undergo significant metabolic and endocrine changes during the transition from pregnancy to lactation, and impaired insulin action influences nutrient partitioning toward the fetus and the mammary gland. Because impaired insulin action during transition is thought to be related to elevated body condition and body fat mobilization, we hypothesized that overconditioned cows with excessive body fat mobilization around calving may have impaired insulin metabolism compared with cows with low fat mobilization. Nineteen dairy cows were grouped according to their average concentration of total liver fat (LFC) after calving in low [LLFC; LFC <24% total fat/dry matter (DM); n = 9] and high (HLFC; LFC >24.4% total fat/DM; n = 10) fat-mobilizing cows. Blood samples were taken from wk 7 antepartum (ap) to wk 5 postpartum (pp) to determine plasma concentrations of glucose, insulin, glucagon, and adiponectin. We applied euglycemic-hyperinsulinemic (EGHIC) and hyperglycemic clamps (HGC) in wk 5 ap and wk 3 pp to measure insulin responsiveness in peripheral tissue and pancreatic insulin secretion during the transition period. Before and during the pp EGHIC, [$^{13}C_6$] glucose was infused to determine the rate of glucose appearance (GlucRa) and glucose oxidation (GOx). Body condition, back fat thickness, and energy-corrected milk were greater, but energy balance was lower in HLFC than in LLFC. Plasma concentrations of glucose, insulin, glucagon, and adiponectin decreased at calving, and this was followed by an immediate increase of glucagon and adiponectin after calving. Insulin concentrations ap were higher in HLFC than in LLFC cows, but the EGHIC indicated no differences in peripheral insulin responsiveness among cows ap and pp. However, GlucRa and GOx:GlucRa during the pp EGHIC were greater in HLFC than in LLFC cows. During HGC, pancreatic insulin secretion was lower, but the glucose infusion rate was higher pp than ap in both groups. Plasma concentrations of nonesterified fatty acids decreased during HGC and EGHIC, but in both clamps, pp nonesterified fatty acid concentrations did not reach the ap levels. The study demonstrated a minor influence of different degrees of body fat mobilization on insulin metabolism in cows during the transition period. The distinct decrease in the glucose-dependent release of insulin pp is the most striking finding that explains the impaired insulin action after calving, but does not explain differences in body fat mobilization between HLFC and LLFC cows.
Key words: glucose metabolism, insulin secretion, insulin responsiveness, endogenous glucose production

INTRODUCTION

The transition period is characterized by dramatic metabolic changes that are targeted at meeting the energy requirements of dairy cows while channeling substrates to the fetus and the mammary glands (Bell, 1995; Bauman, 2000). Because of insufficient feed intake and the resulting negative energy balance during the transition period, cows mobilize body tissue to match their energy demands (Grummer, 1993; Ingvartsen and Andersen, 2000; Drackley et al., 2001). With the onset of lactation, the extreme increase in glucose requirements for milk production results in elevated endogenous glucose production and reduced glucose utilization in peripheral tissues, which provides adequate amounts of glucose for milk synthesis (Bauman, 2000; Drackley et al., 2001; Aschenbach et al., 2010). Enormous variation exists in the degree of fat mobilization around the time of calving, as high-yielding dairy cows follow different metabolic strategies to cover their energy demands during milk production (Kessel et al., 2008; Hammon et al., 2009; Weber et al., 2013). Previously, Tamminga et al. (1997) observed marked

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differences in fat mobilization among cows during the first 8 wk of lactation, ranging from 8 to 57 kg of body fat. Hence, liver fat concentration (**LFC**) shows large inter-individual variations among cows as a function of the increasing plasma concentration of nonesterified fatty acids (**NEFA**) resulting from lipolysis in fat depots and the storage of fat as triglycerides in the liver (Grummer, 1993; Drackley et al., 2001; Hammon et al., 2009).

Insulin plays a key role in regulating energy metabolism during the transition period in dairy cows (Bauman, 2000; Vernon, 2005; De Koster and Opsomer, 2013), and its antilipolytic effect inhibits the release of NEFA during this time (Brockman and Laarveld, 1986; Andersen et al., 2002; Hayirli, 2006). In fact, the transition period is characterized by an insulin-resistant state; namely, reduced insulin sensitivity and responsiveness in distinct peripheral tissues (Bell, 1995; Vernon, 2005; De Koster and Opsomer, 2013), and after calving, there is a decrease in the concentration of plasma insulin (Reist et al., 2003; Hammon et al., 2009; Weber et al., 2013). This reduced insulin status in dairy cows is part of the homeorhetic metabolic regulation that guides nutrients, notably glucose, to tissues that are less dependent on insulin action (e.g., the placenta and the lactating mammary gland; Bell, 1995; Bauman, 2000; Ingvartsen and Andersen, 2000). However, changes in insulin action are tissue-specific and vary among organs and metabolic pathways in ruminants (Faulkner and Pollock, 1990; Vernon, 2005; De Koster and Opsomer, 2013).

In addition, a high body fat content and elevated fat mobilization or administration affect insulin sensitivity and responsiveness (Boden et al., 2002; Pires et al., 2007; De Koster et al., 2015) as well as the secretion of pancreatic insulin (Bossaert et al., 2008; Gupta et al., 2012; Salin et al., 2012). Therefore, dairy cows that exhibit elevated fat mobilization and increased LFC around calving may be exposed to impaired insulin action during the transition period. Pancreatic insulin secretion and insulin responsiveness in peripheral tissues can best be investigated using hyperglycemic (**HGC**) and euglycemic-hyperinsulinemic clamps (**EGHIC**), respectively (DeFronzo et al., 1979; De Koster and Opsomer, 2013). The objective of the present study was to elucidate the effect of variable body fat mobilization around the time of calving on insulin-dependent glucose metabolism, including pancreatic insulin secretion and tissue responsiveness to insulin, in dairy cows during late pregnancy and early lactation. In addition, the insulin-dependent glucose rate of appearance in plasma (**GlucRa**) and glucose oxidation (**GOx**) were investigated postpartum (**pp**). We hypothesized that insulin action around the time of calving is impaired in dairy cows with a greater body fat mobilization and that the extent of impairment differs between late gestation and early lactation.

MATERIALS AND METHODS

Animals, Husbandry, and Feeding

All treatments were conducted in accordance with the guidelines for the use of animals as experimental subjects of the State Government of Mecklenburg-Western Pomerania (Registration No. LALLF M-V/TSD/7221.3-2.1-021/09). For the present study, 20 multiparous German Holstein cows from a local farm were chosen on the basis of their milk yield during one previous lactation (>10,000 kg/305 d) and age (second to fourth lactation). To reduce genetic variation in fat metabolism, all cows were selected for heterozygosity at a polymorphic locus in the acyl-CoA-diacylglycerol acyltransferase 1 gene (*DGAT1* K232A: Lys or Ala at position 232), which affects fat metabolism in muscle and the mammary gland (Thaller et al., 2003).

The present study on insulin-dependent glucose metabolism focused on insulin responsiveness in peripheral tissues and pancreatic insulin secretion, using EGHIC and HGC at wk 5 antepartum (**ap**) and wk 3 pp. The study was part of a comprehensive project regarding energy metabolism and the regulation of feed intake in dairy cows during the transition period (Schäff et al., 2012; Börner et al., 2013). The cows were investigated from wk 7 ap until wk 5 pp; animal management and performance data have been published previously (Schäff et al., 2012; Börner et al., 2013). Cows were kept in tiestalls and fed twice daily for ad libitum allowance with a TMR adapted for the dry period (the far-off diet from wk 7 to wk 4 ap and the close-up diet from wk 3 ap until calving) or lactation. The ingredients and chemical compositions of the different diets were determined according to the recommendations of the German Society of Nutritional Physiology (GfE, 2001, 2008; Table 1).

Cows were grouped according to their mean total LFC on d 3, 18, and 30 after calving in low [**LLFC**; LFC <24% (mean ± SE: 20.0 ± 2.0%) total fat/DM liver tissue; n = 9] and high [**HLFC**; LFC >24.4% (mean ± SE: 30.2 ± 1.8%) total fat/DM liver tissue; n = 10] fat-mobilizing cows. Due to severe sickness during the trial, 1 LLFC cow was excluded from sampling. Changes in LFC during the entire experimental period have been reported by Schäff et al. (2012).

Feed intake in wk 5 ap and wk 3 pp was recorded daily, and BW was measured to calculate DMI per kilogram of BW as well as energy balance (**EB**). Energy balance (expressed in MJ/cow × d) was calculated for