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Effect of hormonal and energy-related factors on plasma adiponectin in transition dairy cows

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ABSTRACT

In transition dairy cows, plasma levels of the insulin-sensitizing hormone adiponectin fall to a nadir at parturition and recover in early lactation. The transition period is also characterized by rapid changes in metabolic and hormonal factors implicated in other species as positive regulators of adiponectin production (i.e., negative energy balance, lipid mobilization) and others as negative regulators (i.e., reduced leptin and insulin and increased growth hormone and plasma fatty acids). To assess the role of onset of negative energy balance and lipid mobilization after parturition, dairy cows were either milked thrice daily (lactating) or never milked (nonlactating) for up to 4 wk after parturition. Plasma adiponectin was 21% higher across time in nonlactating than lactating cows. Moreover, nonlactating cows recovered plasma adiponectin at similar rates as lactating cows even though they failed to lose body condition. Next, we assessed the ability of individual hormones to alter plasma adiponectin in transition dairy cows. In the first experiment, dairy cows received a constant 96-h intravenous infusion of either saline or recombinant human leptin starting on d 8 of lactation. In the second experiment, dairy cows were studied in late pregnancy (LP, starting on prepartum d −31) and again in early lactation (EL, starting on d 7 postpartum) during a 66-h period of basal sampling followed by 48 h of hyperinsulinemic-euglycemia. In the third experiment, cows were studied either in LP (starting on d −40 prepartum) or EL (starting on d 7 postpartum) during a 3-h period of basal sampling followed by 5 d of bovine somatotropin treatment. Plasma adiponectin was reduced by an average of 21% in EL relative to LP in these experiments, but neither leptin, insulin, or growth hormone treatment affected adiponectin in LP or EL. Finally, the possibility that plasma fatty acids repress plasma adiponectin was evaluated by intravenous infusion of a lipid emulsion in nonpregnant, nonlactating cows in the absence or presence of glucagon for 16 consecutive hours. The intralipid infusion increased plasma fatty acid concentration from 102 to over 570 μM within 3 h but had no effect on plasma adiponectin irrespective of presence or absence of glucagon. Overall, these data suggest that energy balance around parturition may regulate plasma adiponectin but do not support roles for lipid mobilization or sustained changes in the plasma concentration of leptin, insulin, growth hormone, or fatty acids.
Key words: energy insufficiency, lipid mobilization, insulin, leptin, growth hormone

INTRODUCTION

Adiponectin is a 30-kDa protein hormone synthesized exclusively by adipose tissue (Kadowaki et al., 2006; Wang and Scherer, 2016). Adiponectin circulates as a homomultimer consisting of low molecular weight, medium molecular weight, and high molecular weight complexes containing 3, 6, or 18 or more adiponectin monomers (Wang et al., 2008; Wang and Scherer, 2016). Adiponectin signals through 2 membrane-bound receptors, adiponectin receptor 1 and adiponectin receptor 2, which are found in most tissues including liver, muscle, and adipose tissue (Kadowaki et al., 2006). Many lines of evidence suggest that adiponectin is an insulin sensitizer. First, decreased plasma adiponectin is observed in conditions and diseases characterized by insulin resistance (**IR**) such as obesity and type 2 diabetes (Kadowaki et al., 2006; Wang and Scherer, 2016). This inverse relation between IR and plasma adiponectin has been found not only in humans but also in various animal models ranging from nonhuman primates to dolphins (Hotta et al., 2001; Venn-Watson et al., 2013). Second, administration of recombinant adiponectin improved insulin action in various mouse models of IR (diet-induced obese, lipoatrophic, db/db, and KKA^{y}; Kadowaki et al., 2006). Third, mutations

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leading to adiponectin loss of function promote IR in both mice and humans (Kadowaki et al., 2006), whereas adiponectin overexpression in ob/ob mice is sufficient to normalize their excessive circulating levels of glucose and insulin (Kim et al., 2007).

We have demonstrated that the plasma concentration of adiponectin varies in a quadratic manner in transition dairy cows with the highest levels in late pregnancy (**LP**), a nadir on the day of parturition, and a progressive return to LP values over the first few weeks of lactation (Giesy et al., 2012; Mielenz et al., 2013). This adiponectin profile occurs in parallel with the development of IR and the onset of negative energy balance (**NEB**) and coincides with rapid reduction in plasma insulin and leptin and reciprocal changes in plasma growth hormone (**GH**) and fatty acids (Block et al., 2001; Rhoads et al., 2004; Giesy et al., 2012). Evidence in rodents and humans indicates involvement of these factors in regulating adiponectin production (Delporte et al., 2004; Bobbert et al., 2009; Lubbers et al., 2013), but whether they contribute to variation in plasma adiponectin in transition dairy cows remains unknown.

The objectives of the present study were to determine first whether the onset of NEB around parturition contributes to reduced plasma adiponectin and second whether sudden changes in the plasma concentrations of leptin, insulin, GH, or fatty acids regulate plasma adiponectin. Our results demonstrate that plasma adiponectin is sensitive to changes in energy balance in the immediate post-periparturient period but rule out leptin, insulin, GH, or fatty acids as factors contributing to reduced plasma adiponectin in transition dairy cows.

MATERIALS AND METHODS

Animals and Design

Samples analyzed were from 5 previous experiments designed to identify effects of variation in energy balance, leptin, insulin, GH, or fatty acids (Block et al., 2001; Leury et al., 2003; Schoenberg et al., 2011; Ehrhardt et al., 2016; Caixeta et al., 2017). All experiments were performed in multiparous Holstein cows at Cornell University and were approved by the Cornell Institutional Animal Care and Use Committee. Procedures common to all experiments included housing in individual stalls and blood collection from chronic intrajugular catheters. Blood was processed to plasma by the addition of sodium heparin (15 IU/mL) and centrifugation. Unless otherwise mentioned, cows were fed unlimited amounts of TMR using automatic feeders and milked daily at 0600 and 1800 h after parturition. Experiments and associated specific procedures were as follows.

Effect of the Periparturient Period and Leptin

The study of Ehrhardt et al. (2016) was used to compare 2 assays in their ability to detect changes in plasma adiponectin between LP and early lactation (**EL**) and to assess the effects of leptin therapy in EL. Ten cows were fed unlimited amounts of TMR formulated for each physiological stage (1.5 Mcal of NE_L and 140 g of CP per kg of DM in LP and 1.5 Mcal of NE_L and 180 g of CP per kg of DM in EL). Plasma adiponectin was analyzed on 4 blood samples collected at 2-h intervals between 0800 and 1400 h in LP (d -29 ± 2, relative to parturition d 0) and again in EL (d +8). After completing blood sampling on d +8, cows were randomly assigned to receive a continuous intrajugular infusion of saline (saline) or human leptin (**hLeptin**, 61 μg/kg of BW/d; Eli Lilly and Company, Indianapolis, IN) for 96 consecutive hours. Plasma adiponectin was measured on 4 samples collected from each cow at 2-h intervals between 88 and 94 h of infusion.

Energy Balance After Parturition

An experiment described in Block et al. (2001) was used to evaluate the effect of positive energy balance after parturition on the recovery of plasma adiponectin. Between parturition and d +32 of lactation, cows were offered a low-energy TMR (1.52 Mcal of NE_L and 189 g of CP per kg of DM) and milked thrice daily at 0900, 1600, and 2300 h (lactating, n = 7) or offered a high-energy TMR (1.70 Mcal of NE_L and 188 g of CP per kg of DM) and never milked (nonlactating, n = 7). Lactating cows were fed ad libitum during the first week postpartum and thereafter limited to amounts consumed on d +7 (13.6 ± 1.2 kg/d); nonlactating cows were fed ad libitum at all times. Each cow was scored for body condition (thin = 1; fat = 5) on wk 1 and 4 by 2 independent individuals as previously described (Block et al., 2001). Plasma variables including adiponectin were analyzed on 4 blood samples collected from each cow every other day between d +5 and +11 and again between d +26 and +32.

Effect of Insulin

The study of Leury et al. (2003) was used to assess the effect of chronic hyperinsulinemia during the transition period on plasma adiponectin. Six cows were fed unlimited amounts of appropriate TMR during LP (1.56 Mcal of NE_L and 140 g of CP per kg of DM) and EL (1.58 Mcal of NE_L and 198 g of CP per kg of DM).