Glucose-Dependent Insulin Response and Milk Production in Heifers Within a Segregating Resource Family Population

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ABSTRACT

An experiment was initiated to evaluate the glucose-dependent insulin response in relation to milk production in F₂ crossbred cattle with respect to secretion type (Holstein) and accretion type (Charolais). For this purpose, F₂ offspring were generated by mating Charolais bulls with German Holstein cows and a following intercross of the F₁ individuals. In 52 dairy heifers of 5 F₂ half-sib families, glucose-dependent insulin responses were investigated during first lactation to test the hypothesis that the different genetic disposition for milk production within the F₂ population would affect the insulin response to glucose. Heifers received intravenous glucose infusions (1 g/kg of BW^{0.75}) 10 d before, and 30 and 100 d after parturition. Blood samples were taken before and at 7, 14, 21, and 28 min after glucose challenge. Glucose and insulin concentrations were measured in blood, and glucose half-life as well as areas under the curve for glucose (AUC_{gluc}) and insulin (AUC_{ins}) were calculated. Milk yield was low but differed among F₂ families. Before parturition, insulin concentrations after glucose challenge showed no between-family differences for AUC_{ins}. In contrast, on d 30 and 100 of lactation, glucose half-life and AUC_{ins} differed among families. Calculated correlations revealed a significant negative relationship between AUC_{ins} and milk yield as well as glucose half-life on d 30 and 100 of lactation. In conclusion, milk production as well as the glucose-dependent insulin response of F₂ Charolais × German Holstein crossbred dairy heifers differed between half-sib families, with both parameters displaying an inverse relation to each other.

Key words: heifer, lactation, glucose metabolism, crossbreeding

INTRODUCTION

Dairy and beef cows differ markedly in milk production and also show differences in the endocrine control

of nutrition partitioning (Bines and Hart, 1978; Veerkamp et al., 2003). Milk production depends on mammary gland development, and therefore on the number of functional epithelial cells and availability of nutrients, especially glucose (Akers, 2000; Shennan and Peaker, 2000; Ingvarsen and Friggens, 2005). Among the hormones, low insulin concentrations along with high growth hormone concentrations are phenotypically associated with high milk yield during lactation (Ingvarsen and Friggens, 2005). Administration of insulin has resulted in depression of milk secretion (Kronfeld et al., 1963). Higher plasma insulin concentrations have been found in beef cows as compared with dairy cows (Hart et al., 1975, 1978; Shingu et al., 2002), and in dairy cows with low genetic merit for milk production vs. high genetic merit (Giesecke et al., 1987; Bonczek et al., 1988; Gutierrez et al., 1999). Therefore, an inverse relationship of insulin concentrations and milk yield seems to exist among different breeds as well as within the same breed. In addition, concentrations of insulin in the plasma of dairy cows were found to be higher before parturition than during lactation (Blum et al., 1973; Walsh et al., 1980; Sartin et al., 1988). These findings indicate that insulin concentrations are related to lactation and to the amount of milk production, but they also raise the question of whether insulin secretion in different metabolic types (dairy vs. beef) depends on milk production.

In Dummerstorf at the Research Institute for the Biology of Farm Animals (FBN), an experiment was initiated using segregating F₂ offspring from the P₀ founder breeds Charolais and German Holsteins. Charolais are known for their distinct nutrient accretion and low milk yield. In contrast, Holsteins are known for their high milk secretion and low tissue accretion of nutrients. Charolais and German Holsteins differ in their properties of nutrient transformation and in their endocrine regulation of nutrient flow (Kühn et al., 2002; Bellmann et al., 2004a,b). This breeding program enabled us to investigate the regulation of nutrient flow in nonlactating and lactating F₂ heifers with a combined dairy and beef genetic background. We hypothesized that the female F₂ offspring of this breeding program

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would differ in their potential for milk production because of a different regulation of nutrient partitioning during lactation (e.g., differences in insulin-independent glucose uptake by the mammary gland) that may be reflected by a variation in glucose-dependent insulin secretion. Although glucose-dependent insulin responses are associated with milk production (Sartin et al., 1985) and insulin is important for nutrient partitioning in cows during lactation (Chilliard, 1999; Bauman, 2000; Drackley et al., 2001), the question of whether glucose-dependent insulin secretion is primarily defined by the rate of milk production or by the random genetic background of the breed has not yet been clarified. Our approach was designed to elucidate whether differences in glucose-dependent insulin secretion are a function of milk production. Alternatively, different levels of glucose-dependent insulin secretion within breeds could be randomly fixed within breed and possibly be unrelated to milk production. To address these questions, glucose tolerance tests (GTT) were performed in F₂ heifers within a segregating family structure to test the hypothesis that insulin response to glucose would show variation within the F₂ population and that the association between milk yield and glucose-dependent insulin response would reflect a functional relationship.

MATERIALS AND METHODS

Animals, Husbandry, and Feeding

The experimental procedures were carried out according to the animal care guidelines of the State Mecklenburg-Vorpommern, Germany, and were approved by the relevant authorities. The crossbred heifers included in our study were generated by mating Charolais bulls (named **A**, **B**, **C**, **D**, and **E**) to German Holstein cows. An intercross of the F₁ individuals was performed using embryo transfer to German Holstein recipients to establish full-sib and half-sib F₂ offspring (Figure 1). This breeding model was chosen to study the genetic and physiological background of phenotypic variability between animals of different nutrient turnover with respect to accretion and secretion type (Kühn et al., 2002). The F₂ heifers comprised 5 paternal half-sibship families, namely, **Ab** (n = 14), **Ba** (n = 10), **Cd** (n = 10), **De** (n = 11), and **Ec** (n = 7). The uppercase letter represents the paternal origin of the F₁ male and the lowercase letter represents the paternal origin of the F₁ female according to the P₀ Charolais sires A, B, C, D, and E. Starting in January 2001, heifers were reared at the FBN research farm at Dummerstorf in a free-stall barn, were inseminated at 18.1 ± 0.4 mo of age with semen from the same sire (German Holstein breed), were calved after 280 ± 0.8 d of pregnancy, and

were milked after parturition twice daily in a milking parlor. First lactation was completed in April 2005. Insulin-dependent glucose metabolism of the F₂ heifers was studied 10 d before parturition and at 30 and 100 DIM.

Before parturition, heifers were fed grass silage ad libitum (235 g of CP/kg of DM and 6.75 MJ of NE_L/kg of DM), 1 kg of concentrates (150 g of CP/kg of DM and 7 MJ of NE_L/kg of DM; mainly barley, sugarbeet pulp, and extracted soybean meal; RM 2007, Vollkraft, Güstrow, Germany) and 300 g of a mineral and vitamin mixture (Salvana 9237, Salvana, Sparrieshoop, Germany). After parturition, heifers received grass silage ad libitum, 3 kg of concentrates, and 300 g of minerals. When milk yield exceeded 15 kg of milk/d, heifers were fed 1 kg of concentrates for every 2 kg of extra milk, respectively.

GTT

Intravenous GTT were performed 2 to 3 h after the morning milking at 30 and 100 d of lactation, and at the same time of day 10 d before parturition (9.2 ± 0.8 actual days). In total, 140 GTT were performed; some GTT were missed or discarded, because heifers were sick at the foreseen date or the antepartum scheduled day was too close to calving. Heifers received jugular cannulas for blood sampling and, after a period of 12 h without food, glucose (1 g/kg of BW^{0.75}) was infused into the jugular vein (Giesecke et al., 1987). Blood samples were taken before and at 7, 14, 21, and 28 min after glucose infusion. Glucose was enzymatically measured immediately after blood sampling in whole blood by the glucosidase method (Ascensia Elite Glucometer, Bayer, Leverkusen, Germany). For insulin, blood samples were collected in tubes containing 1.6 mg of potassium-EDTA/mL of blood (Monovette, Sarstedt, Nümbrecht, Germany) and were placed on crushed ice until centrifuged at 1,500 × g for 20 min at 4°C. Supernatants were aliquoted and plasma aliquots were stored at -20°C until analyzed. Insulin was measured by RIA using a porcine kit (PI-12K, Linco Research, St. Charles, MO; Bellmann et al., 2004a). Cross-reactivity with bovine insulin was 90%. Intra- and interassay coefficients of variation were 4.3 and 8.2%, respectively.

Zootechnical Data

Heifers were weighed during lactation up to 100 DIM. Milk yield was recorded daily, and milk composition was determined weekly. To avoid possible interference of glucose infusion with milk yield on the day of GTT, especially because of feed deprivation before performing the GTT, we summarized the milk yield data of d 27

Figure 1. Pedigree of the segregating resource family at the research institute. Five Charolais bulls (A, B, C, D, and E) were mated to German Holstein cows following intercross of the F_1 individuals to establish full-sib and half-sib F_2 offspring (Ab, Ba, Cd, De, Ec).

to 29 for GTT on d 30 and of d 97 to 99 for GTT on d 100. Milk samples taken routinely once a week (representative sample of morning milking closest to the day of GTT, respectively) were analyzed for milk protein, fat, and lactose contents by an infrared spectrophotometric method (MilkoScan, Foss Germany, Rellingen, Germany) at the local recording association (LKV Mecklenburg-Vorpommern, Güstrow, Germany). Energy-corrected milk was calculated according to Reist et al. (2003).

Statistical Analyses

Data for BW, milk components, and glucose and insulin concentrations are given as means $\pm$ standard errors or pooled standard errors. For glucose and insulin concentrations during GTT, the area under the curves (AUC_{gluc} and AUC_{ins}) was calculated using the GraphPad computer program (GraphPad/Prism User's Guide, GraphPad Software Inc., San Diego, CA). Basal concentrations were subtracted to calculate net AUC values. For calculation of the glucose half-life in blood during GTT, basal concentrations were subtracted and data were subjected to logarithmic transformation prior to linear regression from the 7- to 28-min interval (elimination curve) to calculate kinetic parameters. Half-life (min) was calculated from $\ln 2/k_2$, where k_2 was the slope of the elimination curve. Data were evaluated using the RANDOM and REPEATED methods of PROC MIXED (SAS Institute, 1999). Family and time point

of GTT were used as fixed effects and individual heifers as random effects. To evaluate differences in time patterns within families, the family $\times$ time interaction was included in the model. Differences were localized by Tukey's t -test with $P < 0.1$ for a trend and $P < 0.05$ for a significant difference.

The CORR procedure was used to calculate correlations of glucose and insulin concentrations (basal concentrations, AUC_{gluc} , AUC_{ins}) with milk yield close to 30 and 100 d of lactation (SAS Institute, 1999).

RESULTS

BW and Milk Yield

Body weights were not different between families at the beginning of lactation. Body weights during first lactation increased in all families and differed among families, showing greater ($P < 0.05$) BW in Ab and Cd compared with Ec at 100 DIM (mean BW on d 14 and 100 of lactation were 601 ± 18 and 689 ± 15 , 577 ± 16 and 633 ± 20 , 617 ± 20 and 688 ± 14 , 565 ± 13 and 641 ± 15 , and 550 ± 20 and 605 ± 22 kg of BW for families Ab, Ba, Cd, De, and Ec, respectively).

Milk yield, in general, was low (Table 1). Overall, milk yield and ECM decreased ($P < 0.001$ and $P < 0.05$) from d 30 to 100. Milk fat and milk protein contents increased ($P < 0.05$) and lactose content decreased ($P < 0.05$) during lactation. Milk yield on d 30 and 100 was higher ($P < 0.01$) in Ba than in the other families.

Table 1. Milk yield and composition on d 30 and 100 of lactation in 5 German Holstein × Charolais F₂ crossbred families¹

Trait	Day of lactation	Family					SEM	ANOVA <i>P</i> -values		
		Ab	Ba	Cd	De	Ec		Family	Time	Family × time
Milk yield, kg/d	30	5.8 ^a	13.6 ^b	4.4 ^a	4.9 ^a	5.3 ^a	1.4	0.001	0.001	0.4
	100	3.1 ^a	10.4 ^b	2.3 ^a	3.5 ^a	5.1 ^a	1.3			
ECM, kg/d	30	6.2 ^a	13.7 ^b	4.8 ^a	6.6 ^{ab}	5.5 ^{ab}	1.6	0.001	0.05	0.9
	100	4 ^a	12.6 ^b	2.6 ^a	4.2 ^a	4.4 ^{ab}	1.5			
Milk fat content, g/kg of milk	30	42.5	40.9	40	37.7	40.1	4.4	0.6	0.04	0.9
	100	51.6	46.8	45.2	45.9	41.4	4			
Milk protein content, g/kg of milk	30	34.8	31.8	34.2	35.1	34.6	0.8	0.03	0.01	0.07
	100	38.8 ^a	36.1 ^{ab}	34.4 ^b	35.3 ^{ab}	35.5 ^{ab}	0.8			
Milk lactose content, g/kg of milk	30	45.3	46.9	44.7	46	44.3	1.9	0.2	0.01	0.08
	100	38.9	47.6	38.5	41.2	43.4	2.1			

^{a,b}Means within a row with different lowercase letter are different ($P < 0.05$).

¹Data are presented as means ± pooled SEM.

Energy-corrected milk was higher ($P < 0.05$) in Ba than in Ab and Cd on d 30 and was higher ($P < 0.05$) in Ba than in Ab, Cd, and De on d 100 (Table 1). Although there were no differences between half-sibships regarding milk fat concentration, milk protein content was higher ($P < 0.05$) in Ab than in Cd on d 100 (Table 1).

Basal Glucose and Insulin Concentrations

Basal glucose concentrations (i.e., before glucose infusion) increased ($P < 0.05$) from 10 d before parturition to 30 DIM in all families except Ba. In Ba, basal glucose increased ($P < 0.05$) from 30 to 100 DIM (Table 2). Basal insulin concentrations increased ($P < 0.05$) from 10 d before parturition to 30 DIM in Ab, and increased ($P < 0.05$) from 30 to 100 DIM in Ba. Basal glucose and insulin concentrations remained constant during lactation in all F₂ families except Ba. Glucose and insulin concentrations on d 30 were lower in Ba than in Ab ($P < 0.05$) and Ec ($P < 0.05$; $P < 0.1$ for glucose).

Including all F₂ heifers ($n = 52$), there was a positive correlation between plasma glucose and insulin on d

30 ($r = 0.39$, $P < 0.01$) and 100 ($r = 0.62$, $P < 0.001$) of lactation, but not before parturition. In addition, on d 30 and 100 of lactation, milk yield correlated negatively with plasma glucose ($r = -0.34$, $P < 0.05$ and $r = -0.28$, $P < 0.05$ for d 30 and 100, respectively) and with plasma insulin ($r = -0.3$, $P < 0.05$, $r = -0.49$, $P < 0.001$ for d 30 and 100, respectively).

Glucose-Dependent Insulin Response

Glucose concentrations increased ($P < 0.05$) in all heifers after glucose challenge, but AUC_{gluc} did not differ among families on any day (Figure 2, panels A, C, and E). However, there was an overall time effect ($P < 0.05$), indicating higher AUC_{gluc} concentrations at d 100 of lactation than before parturition. Glucose half-life did not change with time, but was higher ($P < 0.05$) in Ba and Ec than in Ab, De, and Cd during lactation (Table 2). Plasma insulin increased ($P < 0.01$) after glucose challenge in all heifers and indicated a significant family × time interaction. The AUC_{ins} concentrations were lower ($P < 0.05$) at 30 DIM than before partu-

Table 2. Basal glucose (whole blood), plasma insulin concentrations, and glucose half-life during the glucose tolerance test (GTT) on d 10 before parturition and on d 30 and 100 of lactation in 5 German Holstein × Charolais F₂ crossbred families¹

Trait	Day relative to parturition	Family					SEM	ANOVA <i>P</i> -values		
		Ab	Ba	Cd	De	Ec		Family	Time	Family × time
Basal glucose, mmol/L	−10	2.44	2.6	2.4	2.22	2.66	0.16	0.1	0.001	0.06
	30	3.4 ^a	2.7 ^b	3.1 ^{ab}	3.01 ^{ab}	3.5 ^{ab}	0.17			
	100	3.66	3.4	3.28	3.38	3.48	0.23			
Basal insulin, µg/L	−10	0.32	0.36	0.28	0.36	0.38	0.04	0.1	0.001	0.05
	30	0.56 ^a	0.25 ^b	0.42 ^{ab}	0.39 ^{ab}	0.62 ^a	0.06			
	100	0.7	0.54	0.62	0.57	0.6	0.07			
Glucose half-life, min during GTT	−10	20.2	20.6	18.9	25.3	19.7	1.1	0.01	0.3	0.05
	30	19.2	26.1	18.6	19.9	26.2	1.8			
	100	20.7	26.2	19.9	19.2	26.3	1.7			

^{a,b}Means within a row with different lowercase letter are different ($P < 0.05$).

¹Data are presented as means ± pooled SEM.

Figure 2. Concentrations of glucose and insulin in blood during glucose tolerance tests 10 d before parturition (panels A and B) and at 30 d (panels C and D) and 100 d (panels E and F) of lactation in F_2 families of Ab (▼), Ba (△), Cd (○), De (■), and Ec (□).

rition in Ba (Figure 2, panels B and D). The AUC_{ins} did not differ before parturition but on 30 DIM were lower in Ba than in Ab ($P < 0.1$) and Cd ($P < 0.05$; Figure 2D). On d 100, AUC_{ins} were lower ($P < 0.05$) in Ba than in Ab, Cd, and De. In addition, AUC_{ins} were lower in Ec than in Ab ($P < 0.05$) and Cd ($P < 0.1$; Figure 2F).

Including all F_2 heifers ($n = 52$), glucose half-life correlated positively with milk yield on d 30 ($r = 0.42$, $P < 0.01$) and 100 ($r = 0.37$, $P < 0.05$) and correlated negatively with AUC_{ins} on d 30 ($r = -0.44$, $P < 0.01$) and 100 ($r = -0.45$, $P < 0.01$). The AUC_{ins} correlated negatively with milk yield on d 30 ($r = -0.35$, $P < 0.05$) and 100 ($r = -0.54$, $P < 0.001$).

DISCUSSION

Body weight increased during first lactation in all F_2 families. Most likely, F_2 heifers were still growing and, although we did not measure feed intake and did not calculate energy balance, we assumed that F_2 heifers were in a positive energy balance from the beginning of lactation. Milk production in F_2 heifers was predominantly low and consistent with the production of Charolais cows (Jenkins and Ferrell, 1992; Sinclair et al., 1998). Surprisingly, no heifers among the F_2 females yielded milk in amounts closer to milk production of the German Holstein breed. Interestingly, F_2 females of Ba and Ab, which differed markedly in milk production, originated from the same P_0 Charolais bulls. Because sire A was mated to paternal half sisters sired by B and vice versa, this difference in production might indicate possible sex chromosomal or imprinting effects. In addition, mammary gland development is related to growth potential (Sejrsen et al., 2000). In this context we have found the highest growth rates in F_2 males of Ba when compared with males of other F_2 families [H. M. Hammon, R. Pfuhl (FBN, Dummerstorf, Germany), and C. Kühn; unpublished data], possibly indicating a relationship between male growth potential and female mammary gland development within full-sib and half-sib F_2 offspring.

Milk fat and protein contents increased during lactation in F_2 heifers, whereas lactose in milk decreased. Milk composition in beef cows is not well documented, but our data agree with the limited data for Charolais and Holsteins (Sinclair et al., 1998; Reist et al., 2003). The minor changes in milk components among F_2 families might be partly explained by the low milk yield. Because milk composition changes in different milk fractions during milking (Ontsouka et al., 2003), variation of the milk composition possibly increases more in low-yield milkings, where it is difficult to take representative samples. However, variations in milk protein

content might indicate differences in potential for milk protein synthesis among F_2 families.

Changes in basal glucose and insulin concentrations before and during lactation differed from what is known in Holstein dairy cows. In dairy cows, marked decreases of glucose and insulin plasma concentrations were measured during the transition period of lactation (Lomax et al., 1979; Sartin et al., 1988; Reist et al., 2003). In our study, glucose concentrations did not decrease and insulin concentrations decreased only in Ba, the family showing the greatest milk production among the F_2 families. The inverse relationship between basal glucose as well as insulin concentrations and milk production in our study indicated a strong influence of lactation on insulin-dependent glucose metabolism. Similar results were found in most (Hart et al., 1975; Walsh et al., 1980; Gutierrez et al., 1999), but not all (Sartin et al., 1988), previous studies when comparing dairy and beef heifers or cows within the same breed with low and high genetic merit for milk production. Whereas in studies that compare glucose and insulin concentrations and milk production between different breeds, a random, nonfunctional correlation between the parameters because of breed-specific fixation of alleles cannot be excluded, detection of a relation between those traits in an F_2 resource population provides strong support of a functional background. Importantly, differences in plasma insulin among F_2 families were not seen before the onset of lactation. Hart et al. (1978) also reported no differences in plasma insulin concentrations in non-lactating heifers with low and high genetic merit for lactation, supporting the concept that changes in insulin concentrations depend on lactation. Furthermore, the highly positive correlations between glucose and insulin in blood after, but not before, parturition indicated changes in insulin-dependent glucose homeostasis with the onset of lactation in the F_2 heifers.

Although showing no time effects, glucose clearance during GTT was affected by lactation. Interestingly, a higher milk production was associated with an elongated glucose half-life during GTT, and AUC_{gluc} was slightly greater during lactation than before. Lactation therefore affected glucose clearance in F_2 heifers. Insulin responses during GTT differed markedly among F_2 families during lactation, but not before lactation, pointing out the importance of the lactational state for glucose-dependent insulin response. The negative associations between AUC_{ins} and milk production were still present when correlations were calculated without the Ba family, which had the highest milk production (data not shown). Therefore, associations between milk production and glucose metabolism, as described herein, were not based on the different insulin responses of one

F₂ family, which might have been expected from the data presented.

In dairy cows, the glucose-dependent insulin response decreased with the onset of lactation (Sartin et al., 1985; Shingu et al., 2002). The milk-producing mammary gland affects insulin-dependent glucose metabolism, as indicated by a greater fraction of noninsulin-mediated glucose uptake during lactation in dairy cows (Rose et al., 1997). Therefore, lower plasma glucose concentrations during lactation probably caused reduced insulin secretion. It is well known that glucose uptake into the mammary gland in lactating cows and goats is only slightly affected by insulin and that the mammary gland probably does not express insulin-dependent glucose transporters in a significant manner (Laarveld et al., 1981; Zhao et al., 1996; Nielsen et al., 2001). When lactating and nonlactating cows were compared, arterial and portal insulin plasma concentrations as well as pancreatic output and hepatic uptake of insulin were lower after glucose challenge in lactating than in nonlactating cows (Lomax et al., 1979). The high insulin responses after glucose challenge in F₂ heifers with very low milk production or in nonlactating F₂ heifers may have directed glucose to tissues in which glucose transport depends on insulin, that is, skeletal muscle and adipose tissue (Abe et al., 1997). We found a negative association between insulin release and glucose half-life during GTT at 30 and 100 DIM, but not before parturition, suggesting an impaired stimulation of pancreatic insulin secretion through increased plasma glucose during lactation in heifers with relatively high milk production.

The F₂ heifers showing very low milk production had the same insulin release during GTT before and after onset of lactation. Thus, not the physiological state of lactation per se, but the rate of milk production was responsible for insulin release differences between lactating and nonlactating heifers during GTT. As mentioned above, such an inverse relationship between insulin secretion and milk production is well documented in Holstein heifers (Bonczek et al., 1988) and also when comparing dairy and beef heifers or cows (Hart et al., 1975, 1978; Shingu et al., 2002). In our study, we generated a genetic model that combined dairy and beef breeds, but the relationship between plasma insulin concentrations and milk production seemed to be the same as seen for beef and dairy cows (Hart et al., 1978; Bonczek et al., 1988).

In conclusion, milk production in Holstein × Charolais F₂ crossbred heifers was surprisingly low and differed with respect to genetic background. Glucose-dependent insulin response differed among F₂ families during lactation, but not before the onset of lactation, and was inversely related to milk production. Our find-

ings suggest that the genetic capacity for milk production is related to glucose metabolism and affects insulin secretion.

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