Insulin resistance in divergent strains of Holstein-Friesian dairy cows offered fresh pasture and increasing amounts of concentrate in early lactation

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ABSTRACT

The objective of this study was to determine whether the physiological response to an intravenous glucose challenge would be affected by genetic strain or concentrate supplementation in grazing Holstein-Friesian cows in early lactation. North American (NA; $n = 30$) or New Zealand (NZ; $n = 30$) cows were randomly allocated to 1 of 3 feeding treatments. All cows were offered a generous pasture allowance, and 4 of the 6 groups received either 3 or 6 kg of dry matter (DM)/cow per day of concentrates. During wk 5 of lactation, all cows underwent an intravenous glucose challenge. Cows of NA origin produced more milk than NZ cows, but there was no significant strain effect on milk fat or protein yield. Milk yield and the yield of individual components increased with increasing level of concentrate eaten, but there were no significant strain $\times$ diet interactions. During wk 1 to 6, mean body weight and body condition score decreased in all treatments. Average body weight was greater in NA cows, but body condition score was greater for NZ cows. There was no strain or diet effect on the length of the postpartum anovulatory interval, with cows ovulating before 40 d postpartum on average. Glucose fractional turnover rate was greater in NZ cows compared with those of NA origin and in all cows receiving 6 kg of DM concentrates, indicating a less severe insulin resistance in those treatments. Consistent with this, the time taken to dispose of half the peak glucose concentration was less when 6 kg of DM concentrate was fed, and tended to be less in NZ than in NA cows. There was no effect of genetic strain on glucose area under the curve (AUC) at 60 or 120 min, but AUC at both time points was less in cows receiving 6 kg of DM concentrates per day. Neither genetic strain nor nutrition affected basal or peak insu-

lin concentrations, insulin increment, or insulin AUC, and there were no strain $\times$ diet interactions for any of the glucose challenge response variables measured. In conclusion, differences in milk production between NA and NZ cows in early lactation can, at least in part, be explained by the greater degree of insulin resistance in the NA cows, and this insulin resistance can be overcome by supplementing grazing cows with 6 kg of DM concentrates.

Key words: Holstein-Friesian strain, concentrate supplementation, intravenous glucose tolerance test, insulin resistance

INTRODUCTION

Until recently, dairy cow breeding objectives were focused primarily on milk production traits (Miglior, 2005), with little consideration for other traits. Such a policy has resulted in a cow that produces more milk and has a greater propensity to mobilize body condition in early lactation (Buckley et al., 2000; Roche et al., 2006; McCarthy et al., 2007). This greater early-lactation negative energy balance, and a subsequent failure to replenish body energy stores, has been associated with reduced reproductive performance (Beam and Butler, 1999; Buckley et al., 2003; Roche et al., 2007).

Cows of North American (NA) and New Zealand (NZ) origin represent 2 strains of high and low genetic merit for milk production (Roche et al., 2006). Consistent with this premise, previous studies comparing the physical and production characteristics of these 2 genetic strains demonstrated that NA cows produce more milk, have a greater propensity to mobilize body condition in early lactation, partition less energy to improving body condition in mid and late lactation, and, in general, have a lower reproductive performance than NZ cows (Horan et al., 2005; Roche et al., 2006; McCarthy et al., 2007; Macdonald et al., 2008). However, measurements were not taken in any of these studies to determine the physiological mechanisms behind these differences.

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One hypothesis is that these strain differences may be due to an altered response of tissues to insulin and a resultant increased nutrient supply, particularly of glucose and fatty acids, to the mammary gland to support milk production. Insulin resistance exists “whenever normal concentrations of insulin produce a less than normal glucose response” (Kahn, 1978). The availability of glucose to the mammary gland is increased in early lactation because the uptake of glucose by adipose tissue and muscle is reduced, a result of a decrease in the sensitivity of these tissues to insulin (increased insulin resistance; Cronjé, 2000).

Cows of NZ origin fed a TMR have a greater insulin response to a glucose challenge than either NZ cows grazing pasture or NA cows fed TMR or pasture (Chagas et al., 2003), indicating a potential interaction between strain of Holstein-Friesian (HF) cow and diet on insulin resistance in early lactation. These data are consistent with the hypothesis that insulin dynamics may be involved in the effect of genetic strain, nutrition, or both on nutrient partitioning, and may also explain, at least in part, the identified strain effects on reproduction (Chagas et al., 2007a). Despite this awareness of a potential genotype $\times$ environment interaction in insulin resistance, there are no data describing the glucose and insulin responses of grazing dairy cows offered varying amounts of supplements. The objective of this study was to determine whether there are differences in the physiological response of different strains of HF cows to a glucose challenge when grazing pasture and offered increasing levels of concentrate during early lactation.

MATERIALS AND METHODS

The study was conducted at Lye Farm, DairyNZ (Hamilton, New Zealand; 37°46' S 175°18' E) between July and October 2005, and all treatments and measurements were approved by the Ruakura Animal Ethics Committee (Hamilton, New Zealand).

Experimental Design and Treatments

Sixty multiparous HF cows of 2 genetic strains were randomly allocated to 1 of 3 diets in a completely randomized 2 $\times$ 3 factorial design for the first 11 wk of lactation. Groups of 10 cows grazed a generous allowance of fresh pasture (>45 kg of DM/cow per day measured to ground level; approximately 25 kg of DM/cow per day available for consumption) and were supplemented with 0, 3, or 6 kg of DM pelleted concentrate/cow per day (NZ+0, NZ+3, NZ+6, NA+0, NA+3, and NA+6).

Cow allocation ensured that treatments were balanced for age (4.9 ± 1.10 yr), calving date (August 7 ± 18 d). The NA strain ($n = 30$ cows) was of predominantly NA ancestry (minimum of 75%), and the NZ strain ($n = 30$ cows) had a minimum of 75% NZ ancestry.

The cows were sourced from previous strain comparison experiments conducted at DairyNZ (Roche et al., 2006; Macdonald et al., 2008). The mean EBV of the sires used were obtained from LIC (Hamilton, New Zealand) evaluations (May 2005). The EBV for the NZ animals on study were +885 (± 192.4) kg of milk, +34.5 (± 6.1) kg of fat, +32.9 (± 5.8) kg of protein, +57.6 (± 14.3) kg of BW, and +136.6 (± 62.8) d of survival. The mean EBV for the NA animals on study were +1,299 (± 284.0) kg of milk, +32 (± 9.0) kg of fat, +41 (± 6.4) kg of protein, +86.1 (± 14.5) kg of BW, and -14 (± 108.3) d of survival.

Grazing Management and Supplementary Feeding Treatments

Cows were rotationally grazed as 1 herd for the duration of the experiment and were returned to the same area only when a minimum of 2 leaves had appeared on the majority (>75%) of perennial ryegrass tillers. Cows had access to a fresh allocation of pasture daily. Pasture allowance (>45 kg of DM/cow per day) was sufficient to ensure unrestricted DMI of fresh pasture in the unsupplemented cows. Pasture was of high quality throughout the experiment (CP = $22.4 \pm 2.64\%$ DM; OM digestibility = $82.6 \pm 1.42\%$ DM; NDF = $48.3 \pm 4.91\%$ DM; ADF = $22.5 \pm 1.56\%$ DM; lipid = $4.3 \pm 0.12\%$ DM; NSC = $15.7 \pm 3.94\%$ DM; ME = 12.4 ± 0.40 MJ/kg of DM). Quality was maintained throughout the experiment, despite the large grazing residuals, through strategic use of mowing.

Supplementary feeding began 15 d prepartum, with all cows offered 2 kg of DM concentrates per day. After calving, the NZ+3 and NA+3 cows received 3 kg of DM concentrates per day, and the NZ+6 and NA+6 cows were gradually stepped up to 6 kg of DM concentrates per day over the following 4 d (i.e., increments of 1 kg of DM concentrates per day). A flat rate of either 1.5 or 3 kg of DM concentrates (31% crushed barley, 60% crushed maize, 2% wheat middlings, 7% molasses; CP = $12.8 \pm 3.04\%$ DM; NDF = $11.5 \pm 1.49\%$ DM; lipid = $2.7 \pm 0.25\%$ DM; NSC = $65.0 \pm 2.12\%$ DM) was fed individually to the appropriate treatments twice daily during milking.

Measurements

Individual milk yields were recorded daily (Westfalia Surge, Oelde, Germany). Milk fat, CP, and lactose con-

centrations of the milk were determined by a MilkoScan instrument (Foss Electric, Hillerød, Denmark) on individual afternoon and morning aliquot samples collected on 1 d each week. Milk component data were verified by reference techniques for a subset of milk samples (milk fat, Röse-Gottlieb method; CP, Kjeldahl method).

Body weight and BCS were determined weekly after the morning milking. Body condition score was assessed on a 10-point scale, where 1 was emaciated and 10 was obese (Roche et al., 2004). These scores can be converted to a 5-point BCS scale by using a regression equation: 5-point scale = $1.5 + 0.32 \times 10\text{-point scale}$ (Roche et al., 2004).

Intravenous Glucose Challenge

During wk 5 of lactation (33 ± 2.0 DIM), all cows received an intravenous glucose challenge after the morning milking. On the day before the glucose challenge, a catheter (14 gauge $\times$ 19.6 cm; Delmed, New Brunswick, NJ) was inserted into the jugular vein of each cow under local anesthesia to facilitate frequent blood collection. Food was withheld for 12 h before the glucose challenge. Glucose was warmed to body temperature and administered intravenously through the catheter as a 40% solution (Bomac Laboratories, Auckland, New Zealand) at 300 mg of D-glucose/kg of BW and at a constant rate by manually compressing the glucose pack. The infusion of glucose was completed within 2 min, and the catheters were flushed with 50 mL of isotonic saline containing 50 IU/mL of sodium heparin (Mutiparin, CP Pharmaceuticals Ltd., Wrexham, UK). Blood samples were collected at 2 min before the start of the infusion, just before infusion ($t = 0$), every minute from $t = 2$ to $t = 12$ min, and then at 15, 18, 20, 23, 26, 30, 35, 40, 50, 60, 90, 120, 150, 180, 210, and 240 min. All blood samples were collected into 10-mL evacuated blood tubes (Becton Dickinson, Franklin Lakes, NJ) containing 140 IU of sodium heparin, and were immediately placed in ice. Blood samples were centrifuged within 30 min of collection at $1,120 \times g$ and 4°C for 10 min. Aliquots of plasma were stored at -20°C awaiting analysis.

Hormone and Metabolite Assays

Plasma glucose was measured by the hexokinase colorimetric method with a Hitachi 717 analyzer (Roche, Basel, Switzerland) at 30°C by Alpha Scientific Ltd. (Hamilton, New Zealand). The intra- and interassay coefficients of variation were 2 and 4%, respectively. Insulin concentration was measured in duplicate by using double-antibody RIA (Hales and Randle, 1963) validated for bovine plasma (Chagas et al., 2007b).

Insulin antiserum (GP2, 21/7/80), donated by Peter Wynn (Commonwealth Scientific and Industrial Research Organisation, Division of Animal Production, Blacktown, New South Wales, Australia), was raised in guinea pigs by using bovine insulin (BI 4499, Ely Lilly Pty. Ltd., West Ryde, Sydney, Australia). The intra- and interassay coefficients of variation were 3 and 5%, respectively. The limit of detection of the assay was $0.89 \mu\text{IU/mL}$.

Determining Postpartum Anovulatory Interval

Progesterone was measured in a composite of fresh milk samples collected twice each week from calving until cows were confirmed as cycling. Progesterone content was determined by using an ELISA kit (Ridge-way Sciences, Gloucestershire, UK) validated for use in cattle (Sauer et al., 1986). The postpartum anovulatory interval (PPAI) was defined as the interval from calving to the first day that milk progesterone concentration was greater than 3 ng/mL for 2 consecutive sampling days, indicating ovulation (Chagas et al., 2006).

Calculations and Statistical Analyses

Average daily milk production for wk 2 to 11 of lactation was calculated for each cow and analyzed by using linear models that included the factors strain, diet, and the interaction of strain and diet (GenStat 8.2, VSN International Ltd., Hemel Hempstead, UK). Milk, BW, and BCS data for the first week of lactation were omitted from this analysis because the number of days from calving to the first herd test date varied among cows.

To account for repeated measurements through time, BW and BCS data were fitted to spline models within a linear mixed model framework as described by Verbyla et al. (1999). Treatment, linear trend with time, and their interaction were included as fixed effects, and cow, linear trend of time within cow, spline, and the interaction of treatment with spline were included as random effects. Residual maximum likelihood in GenStat 8.2 was used to fit these models. When interactions between time and treatment were not significant, the means over the trial period are presented.

The patterns of plasma glucose and insulin during the glucose challenge were analyzed by using the methods described by Kaneko (1989) and Opsomer et al. (1999). Glucose tolerance was estimated by calculating parameters that describe the clearance of the infused glucose. The fractional turnover rate (k), the half-life ($T_{1/2}$; the time required for glucose concentration to fall by one-half), and the area under the curve (AUC) at 60 and 120 min (T_{60} and T_{120} , respectively) after

Table 1. Average daily milk, fat, protein, and lactose yields (kg), BW (kg), BCS, and postpartum anovulatory interval (PPAI; d) for New Zealand (NZ) and North American (NA) Holstein-Friesian dairy cows fed 0, 3, or 6 kg of DM concentrates/cow per day during the first 11 wk postpartum

Item	Strain			Diet				P-value		
	NZ	NA	SED	0	3	6	SED	Strain	Diet	Strain × diet
Milk yield	30.8	33.9	1.32	28.5	32.4	36.1	1.61	<0.05	<0.001	0.37
Fat yield	1.3	1.3	0.05	1.2	1.3	1.4	0.07	0.70	<0.05	0.69
Protein yield	1.1	1.1	0.04	0.9	1.1	1.2	0.05	0.10	<0.001	0.43
Lactose	1.5	1.6	0.06	1.4	1.6	1.7	0.08	<0.05	<0.001	0.38
BW	515	544	13.86	524	527	539	16.69	<0.05	0.67	0.50
BCS ¹	4.4	3.9	0.09	4.0	4.2	4.2	0.16	<0.001	0.42	0.85
PPAI	35	38	4.14	41	33	35	4.01	0.85	0.83	0.92

¹BCS measured on a 10-point scale, where 1 is emaciated and 10 is obese; Roche et al., 2004.

infusion, beginning at T_5 (5 min after infusion started), were calculated:

$$k\text{-value, } \%/min = 100 \times [(\log \text{ glucose } T_{15} - \log \text{ glucose } T_{45}) / (T_{45} - T_{15})];$$

$$T_{1/2}, \text{ min} = 100 \times (0.693/k).$$

The insulin response to the glucose infusion was determined. The insulin peak is attributed to insulin release by pancreatic β -cells and was illustrated by peak insulin concentration, insulin increment (insulin peak level – basal insulin level), and AUC between T_5 and T_{60} (calculated as $T_{60} - T_5$) and between T_5 and T_{120} (calculated as $T_{120} - T_5$).

The parameters generated from the glucose and insulin profiles were analyzed by using linear models in GenStat 8.2. The association between PPAI and the model parameters was obtained by using the CENSOR procedure in GenStat 8.2.

RESULTS

Milk Production, BW, BCS, and PPAI

Mean milk production data for the 11-wk experimental period are presented in Table 1. Milk yield and the yields of protein, fat, and lactose increased with increasing level of concentrate eaten.

Cows of NA origin produced more ($P < 0.05$) milk and lactose than NZ cows, but there was no strain effect on daily fat or protein yield. No strain × diet interactions were evident in milk yield or in yield of protein, fat, or lactose (Table 1).

From wk 1 to 6, mean BW and BCS decreased in all treatments. Average BW was greater ($P < 0.05$) in NA cows during the 11-wk experimental period, but mean BCS was greater ($P < 0.001$) for NZ cows (Table 1). No significant strain × diet interactions were evident

in either BW or BCS. No strain or diet effect on the length of the PPAI was evident, with the average PPAI for all cows being 37 d (Table 1).

Glucose Challenge

The effects of strain and diet on the response of dairy cows to a glucose infusion are presented in Table 2. Basal glucose concentrations did not differ between strains, but cows receiving 3 kg of DM concentrates per day had greater basal plasma glucose concentrations compared with cows on the other 2 nutrition treatments (Table 2).

The fractional turnover rate of glucose was greater ($P < 0.05$) in NZ cows compared with those of NA origin. Diet also influenced glucose fractional turnover rate ($P < 0.01$); k was greater in cows offered 6 kg of DM concentrates than in cows on either of the other 2 treatments, which did not differ from each other.

The time taken to dispose of one-half the peak glucose concentration ($T_{1/2}$) tended ($P = 0.08$) to be greater in NA cows than in NZ cows (Table 2), but to be less in cows offered 6 kg of DM concentrates ($P < 0.05$; Table 2). No effect of genetic strain was evident on glucose AUC at T_{60} or T_{120} , but these parameters decreased ($P < 0.01$) with increasing level of supplementation.

Basal insulin concentrations were not significantly different across strains or diets, and there was no significant effect of strain or diet on peak insulin concentration, insulin increment, or insulin AUC at T_{60} or T_{120} (Table 2). No strain × diet interactions were evident in any of the glucose challenge response variables measured (Table 2). Correlations among glucose and insulin variables with PPAI were not statistically significant (Table 3).

DISCUSSION

The hypothesis that the glucose and insulin responses to an intravenous glucose challenge would be affected

Table 2. Response variables to an intravenous glucose tolerance test in New Zealand (NZ) and North American (NA) Holstein-Friesian dairy cows fed 0, 3, or 6 kg of DM concentrates/cow per day at 5 wk postpartum

Item	Strain			Diet				P-value		
	NZ	NA	SED	0	3	6	SED	Strain	Diet	Strain $\times$ diet
Basal glucose, mmol/L	3.5	3.5	0.11	3.4	3.7	3.4	0.13	0.95	<0.05	0.90
Fractional turnover rate, %/min	2.0	1.8	0.09	1.8	1.8	2.2	0.12	<0.05	<0.01	0.21
Glucose half-life, min	35	39.5	2.16	39.7	39.9	33.2	2.63	0.08	<0.05	0.34
Glucose AUC ¹ T ₆₀ ² , mmol	400	402.3	11.77	418	409	376	14.39	0.86	<0.01	0.65
Glucose AUC T ₁₂₀ ³ , mmol	601	604	18.85	628	617	563	23.05	0.89	<0.01	0.74
Basal insulin, μ IU/L	3.1	2.9	0.49	3.0	3.3	2.6	0.61	0.78	0.55	0.97
Insulin peak, μ IU/L	66	62	7.19	63.6	60.4	67.9	8.79	0.51	0.69	0.95
Insulin increment, μ IU/L	63	59	7.02	60.5	57.1	65.3	8.59	0.52	0.63	0.94
Insulin AUC T ₆₀ , μ IU	1,888	1,794	207.0	1,936	1,702	1,873	253.2	0.65	0.63	0.90
Insulin AUC T ₁₂₀ , μ IU	2,140	2,055	238.3	2,264	1,926	2,086	291.4	0.72	0.50	0.82

¹AUC = area under the curve.²Time from 5 to 60 min (T₆₀) after glucose infusion.³Time from 5 to 120 min (T₁₂₀) after glucose infusion.

by cow genetic strain, modified by the amount of concentrate supplementation, or both is supported by the presented data. A greater rate of glucose disposal in cows of NZ origin, compared with NA cows, and in those receiving 6 kg of DM concentrates/cow per day, and the lack of strain or diet effects on the plasma insulin profile postchallenge indicate that NA cows were more insulin resistant than NZ cows in early lactation, and that supplementing cows with 6 kg of DM concentrates per day reduced insulin resistance, irrespective of the strain.

In the present study, a frequently sampled intravenous glucose tolerance test was used as an indirect method to measure insulin resistance (Bergman et al., 1979). The variables calculated from the glucose and insulin profiles (e.g., k , T_{1/2}, and AUC) were quantitatively similar to those presented by Opsomer et al. (1999) and Pires et al. (2007) for TMR-fed cows when a similar glucose dose rate per kilogram of BW was used. The clearance of the infused glucose, defined by k and T_{1/2}, increased when 6 kg of DM concentrate was fed and, as a result, the time to dispose of circulating glucose was shortened. These results and the greater milk production in NA cows indicate that genetic selection for increased milk production has resulted in peripartum homeostatic changes that facilitate the supply of energy to the mammary gland at the expense of peripheral tissues, resulting in greater rates of BCS mobilization. These data are consistent with full-lactation studies (Buckley et al., 2000; Roche et al., 2006; McCarthy et al., 2007; Macdonald et al., 2008), in which cows of NA origin had greater postcalving BCS loss, lower average BCS and nadir BCS, and greater energy output in milk than NZ cows, irrespective of the feeding system; this is consistent with their greater EBV for milk yield (+1,299 and 885 kg for NA and NZ HF, respectively).

Previous research by this group (Chagas et al., 2003) reported an effect of nutrition on the insulin response to a glucose challenge, with NZ cows fed a TMR exhibiting greater insulin concentrations in response to a glucose challenge than NZ cows fed pasture. These results are consistent with Xing et al. (1991), who reported that cows fed NSC have a greater insulin response when submitted to a glucose challenge and have a faster glucose disposal. This effect of diet on the insulin response to a glucose infusion was not observed in the present study, suggesting that the amount or type of concentrate offered or the method of feeding (TMR or fed twice daily at milking) may have had an effect on the insulin response to the glucose infusion.

The greater glucose disposal rate and shorter glucose half-life in the cows fed 6 kg of DM concentrate compared with pasture-fed cows or those fed 3 kg of DM concentrate indicates that there may also be a threshold level of dietary NSC required to increase peripheral tissue sensitivity to insulin. Such a hypothesis

Table 3. Associations among glucose and insulin response variables and postpartum anestrus interval

Variable name	r ²	P-value ¹
Fractional turnover rate	0.009	0.79
Glucose half-life, min	0.016	0.53
Glucose AUC ² T ₆₀ ³	0.015	0.59
Glucose AUC T ₁₂₀ ⁴	0.028	0.34
Insulin peak	0.012	0.41
Insulin increment	0.011	0.43
Insulin AUC T ₆₀	0.007	0.43
Insulin AUC T ₁₂₀	0.006	0.41

¹Pooled within treatment.²AUC = area under the curve.³Time from 5 to 60 min (T₆₀) after glucose infusion.⁴Time from 5 to 120 min (T₁₂₀) after glucose infusion.

of a threshold level of NSC to induce insulin resistance is consistent with the profiles of BCS loss in NA cows reported by Roche et al. (2006). Their results indicated an interaction between genetic strain and nutrition in the partitioning of energy toward BCS, with a positive linear effect of NSC on BCS gain in NZ HF cows, but a threshold amount of dietary NSC required in NA HF before energy was directed toward BCS replenishment. Such an insulin-resistance threshold or switch has not been reported previously and requires further investigation to determine the threshold level relative to genetic merit for milk production, and whether the effect is dependent on supplement type.

In dairy cows, the whole-body utilization of glucose is primarily insulin independent (Rose et al., 1997). In particular, uptake of glucose by the mammary gland is controlled by GLUT-1 transporters, acting independently of insulin. In the state of insulin resistance, the metabolic signals of insulin in the liver, muscle, and adipose tissues are said to be selectively impaired (Berson and Yalow, 1970). This is an evolutionary adaptation of mammals to ensure that nutrient supply for the neonate is prioritized postpartum above maintenance of tissue reserves. This hypothesis is consistent with the periparturient homeorhetic changes that occur to prioritize milk production (Bauman and Currie, 1980), including the upregulation of GLUT-1 transporters in early lactation (Zhao and Keating, 2007). Intensive genetic selection for milk production is likely to have furthered this evolutionary drive toward prioritization of energy for milk production, consistent with the greater early-lactation insulin resistance in NA cows, which have undergone more intensive selection for milk production.

Previous reports on the positive effects on PPAI of supplementing cows pre- or postcalving (Chagas et al., 2006; Burke and Roche, 2007) can be attributed to supplementing underfed cows, or to an effect of prepartum nutrition on calving BCS. In the present study, all cows were offered an unrestricted allowance of highly digestible fresh pasture and there was no difference in calving BCS. Therefore, it was possible to investigate the effect of insulin resistance on PPAI. Despite noted differences in insulin resistance, all cows ovulated within 40 d of calving when offered generous allowances of pasture, and there was no relationship between the measured glucose disposal parameters and PPAI; these data reflect a lack of relationship between insulin resistance and the duration of the PPAI.

In conclusion, milk production and energy balance differences associated with genetic selection for milk production can, at least in part, be attributed to a greater degree of insulin resistance. Results indicate that early-lactation insulin resistance can be partially

overcome by supplementing cows with NSC-based concentrates. However, data also indicate a potential threshold amount of NSC required to achieve this effect.

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