MANAGING METABOLISM OF TRANSITION DAIRY COWS THROUGH NUTRITION

Thomas R. Overton, Ph.D.
Department of Animal Science
Cornell University
Ithaca, NY 14853

TAKE HOME MESSAGES

- Transition cows must exquisitely coordinate their metabolism to meet tremendous increases in nutrient demand during early lactation. These adaptations include adaptations in whole-body glucose metabolism and liver-specific adaptations relative to utilization of individual substrates for glucose synthesis.
- Mobilization of nonesterified fatty acids (NEFA) from body fat during the transition period appears to present challenges to the capacity of liver to synthesize glucose, either directly or indirectly through impaired capacity of liver to detoxify ammonia to urea.
- Opportunities to manage metabolism of NEFA and improve metabolic health of transition cows exist both through supply-side manipulations and potentially through nutritional modulation of pathways of fat metabolism within liver.

INTRODUCTION

The transition period of the lactation cycle in dairy cattle is characterized by dramatic changes in nutrient demand that necessitate exquisite coordination of metabolism to meet requirements for energy, glucose, and amino acids by the mammary gland following calving. Estimates of demand for glucose, amino acids, fatty acids, and net energy by the pregnant uterus at 250 days of gestation and the lactating mammary gland at 4 days postpartum have been presented previously (Bell, 1995) and indicate approximately a tripling of demand for glucose, a doubling of demand for amino acids, and approximately a 5X increase in demand for fatty acids during this timeframe. The cow in turn relies on metabolic controls to enable these changes in nutrient partitioning to occur. The two critical metabolic adaptations underpinning successful transitions to lactation are:

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1) The cow alters her glucose metabolism to meet the dramatically increased glucose demand after parturition.
2) The cow mobilizes large amounts of body fat in support of lactation; however, this also can have negative ramifications for liver function and metabolic health.

The liver plays a central role in both of these critical adaptations; therefore, the remainder of this paper will integrate changes that occur in the physiology of the liver in the context of these major metabolic adaptations and provide some insight into "managing metabolism" on commercial dairy farms.

ADAPTATIONS OF LIVER METABOLISM IN TRANSITION COWS

The liver is one of the most metabolically active tissues of the ruminant, utilizing approximately 25% of whole-body oxygen consumption while accounting for only about 2% of body weight (Huntington and Reynolds, 1987). Because essentially all nutrients absorbed from the gastrointestinal tract must pass through it, the liver has a major influence on the quantities and types of nutrients that are supplied to the peripheral tissues for maintenance and productive functions. Because of this place at the crossroads of metabolism, it is a logical candidate for regulation during the transition period. Data in Table 1 indicate that liver size does not change greatly during the transition period; however, oxygen uptake (an indicator of metabolic activity) measured at similar timepoints is approximately doubled during early lactation compared with the late dry period.

Table 1. Liver mass (wet weight) and oxygen uptake by liver tissue during the transition period (Reynolds et al., 2000a; 2000b).

	Day relative to calving			
	-21	-7	10	22
Liver weight, kg	9.0	8.8	8.8	9.6
	Day relative to calving			
	-19	-11	11	22
Oxygen uptake, moles/d	35.4	38.8	75.8	80.1
Oxygen uptake per unit of tissue, moles/(kg•d)	3.9	4.4	8.6	8.3

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Glucose metabolism in the transition cow

At least some of this increased metabolic activity is a result of increased gluconeogenesis by the liver after calving. Glucose represents an overriding metabolic demand during the transition period because of the requirements of the mammary gland for lactose synthesis. Calculated glucose supply based upon intestinal absorption and hepatic gluconeogenesis from substrates derived from dietary sources is approximately 500 grams per day less than demand during the first three weeks or more postcalving (Figure 1).

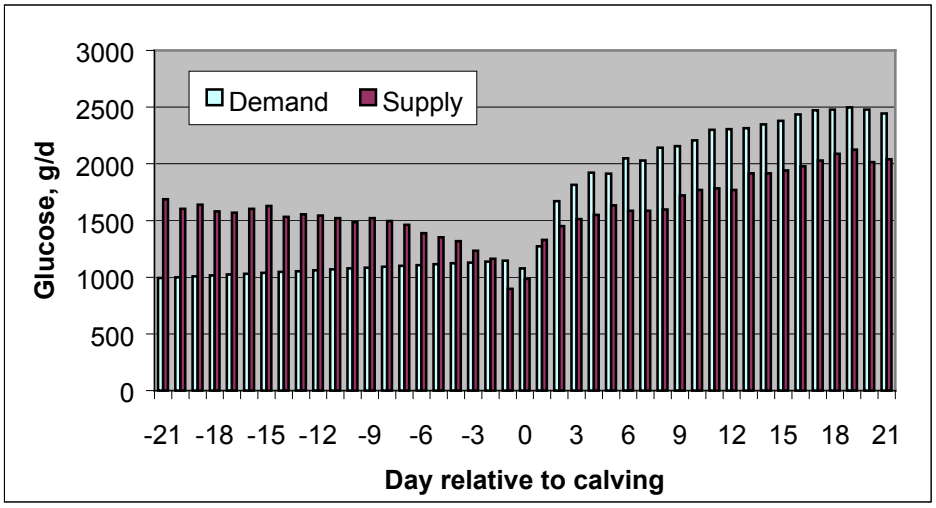

Figure 1. Predicted whole-body glucose demand and supply during the transition period in dairy cows using performance data of Piepenbrink and Overton (2000) and approach of Overton (1998).

Recently, data were obtained using cows surgically fitted with multiple blood sampling catheters in the venous drainage of the gut and liver that enable us to compare our estimates of glucose supply and demand with actual supply (Figure 2). These data indicate that our predicted glucose requirement of approximately 1000 grams per day during the closeup dry period matches reasonably well with both predicted and actual supply of glucose during this timeframe. After calving, the predicted requirement for glucose more than doubles, and predicted supply lags calculated demand by 383 and 350 grams per day at 11 and 22 days postpartum, respectively. The actual supply of glucose is much greater than the predicted supply, indicating that sources other than those accounted for by digestible energy intake are making contributions to liver glucose output

during this timeframe. Recent data (Overton et al., 1998) suggest that at least part of the additional glucose is being synthesized from amino acids during early lactation.

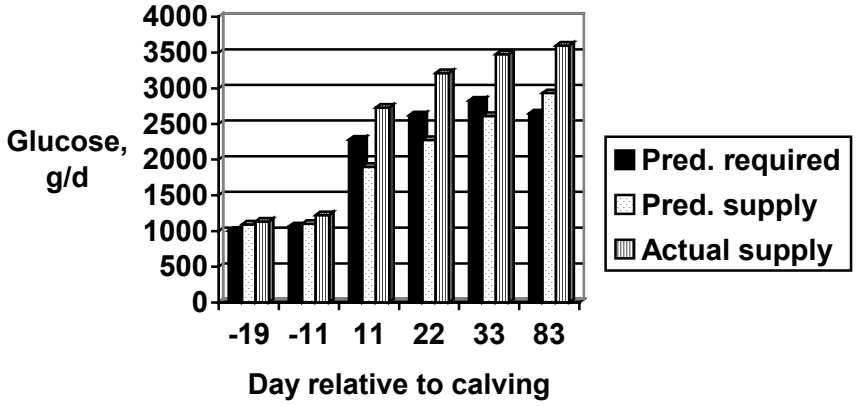

Figure 2. Predicted whole-body glucose requirements compared with predicted and actual supply of glucose by gut and liver during the transition period and early lactation. Data are from Reynolds et al. (2000a). Predictions are as described by Overton (1998).

In summary, liver metabolism in transition dairy cows can be characterized by a dramatic increase in metabolic activity that accompanies the large increase in gluconeogenesis during early lactation compared with the late dry period. Available data indicate that substrate utilization for gluconeogenesis by liver is modulated during this timeframe, and certainly impinge on nutrient requirements of transition cows. Calculations of glucose supply based solely upon energy intake underpredict actual glucose output by liver during early lactation; therefore, other sources such as amino acids must contribute to glucose synthesis during this timeframe.

Mobilization of body fat and ramifications for liver and metabolic health during the transition period

Mobilization of body fat occurs through release of nonesterified fatty acids (NEFA) into the blood (Figure 3). These NEFA are used for energy by body tissues and as precursors for synthesis of milk fat; however, available data suggest that the liver takes up NEFA in proportion to their

supply (Emery et al., 1992). Unfortunately, the liver typically does not have sufficient capacity to completely dispose of NEFA through export into the blood or catabolism for energy (Figure 3). When nutrient intake is insufficient and large amounts of NEFA are released into the blood, the liver begins to accumulate and store NEFA as triglycerides, thus leading to fatty liver in varying degrees.

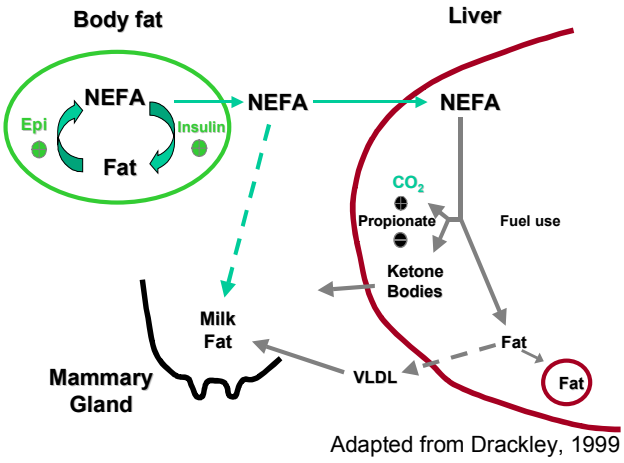

Figure 3. Schematic of metabolism of nonesterified fatty acids (NEFA) in the dairy cow (adapted from Drackley, 1999).

It is likely that a certain amount of triglyceride accumulates in liver of almost all high-producing cows during the first few weeks postpartum. What is uncertain is the threshold at which fat begins to have detrimental effects on other processes in liver. Cadorniga-Valino et al. (1997) demonstrated that fat infiltration of isolated hepatocytes decreased gluconeogenic capacity of the tissue (Figure 4). A followup experiment using a "physiological" mixture of fatty acids determined that fat infiltration did not affect rates of gluconeogenesis, but decreased ureagenic capacity, the process through which ammonia is detoxified to urea (Figure 5; Strang et al., 1998).

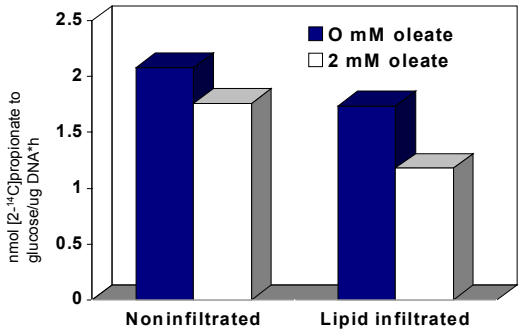

Figure 4. Fat infiltration or concurrent presence of oleate decreases the capacity of liver cells to synthesize glucose from propionate (Cadorniga-Valino et al., 1997).

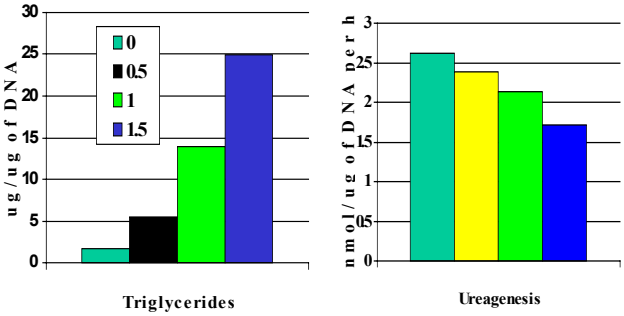

Figure 5. Triglyceride accumulation in liver cells decreases their capacity to detoxify ammonia to urea (Strang et al., 1998).

The implications of decreased ureagenic capacity are not clear, but limited evidence suggests that this phenomenon may occur in dairy cows during the transition period. Zhu et al. (2000) determined that peripheral concentrations of ammonia doubled when liver triglyceride concentrations increased during the first 2 d postpartum (Table 2). Incubation of isolated hepatocytes with ammonium chloride in vitro strongly inhibited their capacity to synthesize glucose from propionate (Figure 6; Overton et al., 1999). Therefore, it is conceivable that inhibition of gluconeogenesis may occur in vivo when triglycerides accumulate in liver; the mechanism

perhaps is modulated by ammonia supply to liver. Potential implications for the management of transition dairy cows center around carbohydrate and protein nutrition. As discussed previously, significant quantities of amino acids are needed for gluconeogenesis. However, excess protein or poorly balanced protein relative to carbohydrate supply may increase the ammonia load on the animal, and thereby affect the capacity of liver to synthesize glucose.

Table 2. Plasma concentrations of urea and ammonia in peripheral blood around calving and their relation to liver triglyceride (Zhu et al., 2000).

Time relative to calving	Ammonia (μM)	Urea (mg/dl)	Liver TG, %
- 27 days	33.4	5.96	2.58
+ 12 hours	61.1	6.34	. . .
+ 16 hours	64.8	6.08	. . .
+ 22 hours	44.2	5.78	13.10
+ 35 days	28.1	5.68	7.89
Standard error	5.5	0.35	2.81

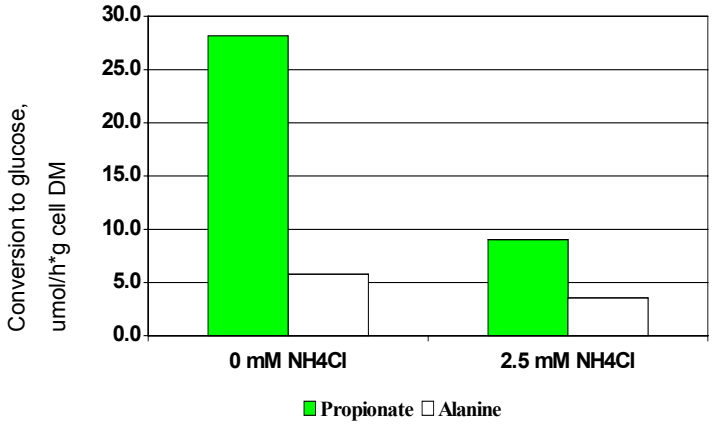

Figure 6. Conversion of [1-^{14}C]propionate and [1-^{14}C]alanine to glucose by isolated liver cells as affected by addition of NH_4Cl in vitro (Overton et al., 1999).

STRATEGIES TO MANAGE LIVER METABOLISM IN TRANSITION COWS

Our guiding principle based collectively upon these data is that management of NEFA during the transition period is an important factor influencing liver health, the capacity of liver to make glucose, and subsequently production and metabolic disorder incidence in transition cows. The two primary approaches that can be taken are:

1) decrease the supply of NEFA to liver through diet and feeding management (perhaps use of glucogenic supplements)
2) optimize capacity of liver to dispose of NEFA either by burning them for fuel or exporting them as triglycerides in lipoproteins (VLDL)

Good closeup and fresh cow nutritional programs, combined with excellent feeding management to achieve high levels of dry matter intake throughout the transition period, achieves 80 to 90% of the potential of the first strategy and should always be the first area of focus for management. Glucogenic supplements such as propylene glycol are effective at decreasing concentrations of NEFA and B-hydroxybutyrate (BHBA; the predominant ketone body found in blood); however, propylene glycol must be drenched in order to be effective and thus presents both cost and labor challenges. The duration of treatment in most experiments reported in the literature ranges from 10 to 40 days per cow. Recently, two experiments have been conducted (Pickett et al., 2001; Stokes and Goff, 2001) that report beneficial effects of drenching propylene glycol beginning on the day of calving and continuing for one or two subsequent days -- these short-term treatments are much more acceptable from a cost and labor standpoint and have more potential for commercial application.

Recently, another strategy related to decreasing energy demands on the transition cow has been suggested to potentially decrease reliance on body reserves and thereby reduce the supply of NEFA to the liver. In typical midlactation cows, approximately 50% of the fatty acids secreted as milk fat are taken up by the mammary gland from the bloodstream as preformed fatty acids. The remaining 50% of fatty acids in milk are synthesized de novo in the mammary gland, and account for approximately 50% of the energetic cost of milk synthesis (NRC, 2001). Conjugated linoleic acids (CLA), specifically the *trans*-10, *cis*-12 isomer of CLA, have been discovered to be potent inhibitors of milk fat synthesis

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(Bauman et al., 2000). Giesy et al. (1999) fed cows 50 g/d of a mixture of CLA isomers (35% *trans*-10, *cis*-12 by weight) in a Ca-salt form from d 13 through 80 postpartum. They reported few effects of CLA supplementation on cow performance during d 14 through 28 postcalving; however, milk yield was increased, and percentage and yield of milk fat were decreased, during d 35 through 80 postpartum. Energy balance was not affected by treatment during either period. Given that supplementation with CLA in their experiment began after concentrations of NEFA have returned to relatively low levels in the blood (Overton and Piepenbrink, 1999), we hypothesized that supplementation of CLA during the entire transition period and early lactation would be more effective in terms of potentially decreasing energy demand during early lactation. Bernal-Santos et al. (2001) fed cows 42.8 g/d of a mixture of CLA isomers (29% *trans*-10, *cis*-12 by weight) in a Ca-salt form from 14 days before expected calving through 140 days of lactation. Results were similar to those of Giesy et al. (1999) in that milk yield and milk fat percentage during the first two weeks postpartum were not affected by CLA supplementation; however, milk fat percentage was decreased by 13% and milk yield tended to be increased (6.6 lb/day) during the entire postpartum period in cows administered the CLA supplement. Energy balance and concentrations of NEFA and BHBA in plasma were not affected by treatment. Therefore, contrary to our hypothesis, CLA supplementation does not appear to substantially reduce reliance on body fat stores; however, energy spared from milk fat synthesis apparently was redirected to lactose synthesis and may offer the opportunity to use CLA as a management tool to increase peak milk yield.

Even when the first strategy is in place on individual dairy farms, we believe that there are opportunities to further improve liver health by employing nutritional strategies to optimize the capacity of liver to dispose of NEFA rather than accumulate them as fat in liver tissue. As mentioned above, the two disposal routes of NEFA from liver involve burning them for fuel and exporting them back into the blood as triglycerides in very low density lipoproteins (VLDL; Figure 3). It is beyond the scope of this paper to review the complex biochemistry underlying each of these pathways. The reader is referred to reviews by Drackley (1999), Gruffat et al. (1996), and Overton and Piepenbrink (1999) if more detail on the biochemistry is desired.

Evidence from metabolic incubations conducted with liver slices in vitro indicated that use of NEFA for fuel is sensitive to carnitine supply.

Carnitine is a quasi-vitamin that is required for transport of NEFA into the mitochondria where they are oxidized. Carnitine can be supplied through the diet or synthesized in the cow from methionine and lysine, typically considered to be the two most limiting amino acids for milk synthesis in the cow. Experiments evaluating whether liver use of NEFA for fuel is sensitive to dietary supplies of carnitine or methionine and lysine have not been conducted.

The second pathway that has potential for nutritional modulation is export of NEFA as VLDL. Ruminant capacity for synthesis and secretion of VLDL is much lower than nonruminant species. The pathway of VLDL synthesis is complicated, and involves a number of different metabolites that must be present in order to successfully synthesize and secrete a VLDL particle into the blood. French workers (see review by Gruffat et al., 1996) have focused on factors affecting synthesis of the protein called apolipoprotein B100 (apo B), which is required for stabilization of the VLDL particle. They have determined that export of VLDL appears to be sensitive to supply of Met and Lys; the mechanism appears to be related to synthesis of apo B (Bauchart et al., 1998).

Chickens and some other nonruminant species accumulate fat in their livers if they are fed diets devoid of the quasi-vitamin choline. Choline (as phosphatidylcholine) is required as a neurotransmitter and as a component of cell membranes. Phosphatidylcholine is also required in these species for synthesis and secretion of VLDL. Thus, we were interested in determining whether the pathways of NEFA metabolism in liver of the transition cow are sensitive to choline supply.

Ruminants derive choline from microbial synthesis in the rumen. To what extent rumen microbes supply choline is not certain. Because choline fed either as choline chloride or within feedstuffs is rapidly degraded in the rumen, choline supply to the ruminant can only be meaningfully increased if the choline is fed in a rumen-stable form. We conducted an experiment to determine whether supplementing increasing amounts of rumen-stable choline (Reashure™, Balchem Corporation, Slate Hill, NY) to diets of transition cows affects liver disposal of NEFA and in turn decreases triglyceride accumulation in liver tissue (Piepenbrink and Overton, 2000). Samples of liver tissue were obtained via biopsy at 21 days before expected calving and on days 1 and 21 postpartum. Conversion of [1-^{14}C]palmitate to CO_2 (indicator of use of NEFA for fuel) was not affected by choline supplementation; however, the rate of conversion of [1-

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^{14}C]palmitate to stored esterified products (index of rate of accumulation of NEFA as fat within liver tissue) decreased linearly with choline supplementation (Figure 7). Triglyceride concentration of liver tended to decrease linearly with choline supplementation, and the concentration of glycogen in liver increased linearly with choline supplementation during the transition period (Table 3). Arithmetic derivation of the ratio of triglyceride to glycogen in liver based upon the least squares means for each parameter indicates that this ratio decreased as the amount of choline supplemented to the diet increased. This ratio has been implicated as an indicator of susceptibility to clinical ketosis (Drackley et al., 1992); therefore, our data would suggest that cows fed diets supplemented with choline during the transition period were less susceptible to developing clinical ketosis compared with the controls. In summary, these data suggest indirectly that choline supplementation may modulate the capacity of liver to export NEFA as triglycerides in VLDL.

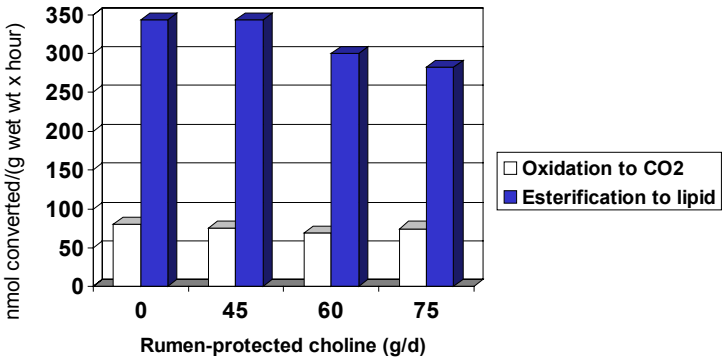

Figure 7. Conversion of [1-^{14}C]palmitate to CO_2 and esterified products by liver slices from cows fed increasing amounts of rumen-protected choline (Piepenbrink and Overton, 2000).

Table 3. Composition of liver samples obtained from cows consuming different amounts of rumen-protected choline from 21 days prepartum through 63 days postpartum (Piepenbrink and Overton, 2000).

	Rumen-protected choline, g/d					
Item	0	45	60	75	SE	Effect
Triglyceride, % wet weight	15.6	14.9	13.2	11.4	2.21	Linear trend of choline supply
Glycogen, % wet weight	0.79	0.81	1.12	1.40	0.21	Linear effect of choline supply
Triglyceride: Glycogen	19.7	18.4	11.8	8.2		

It is likely that interrelationships exist among choline, methionine, and the analog of methionine in the ruminant. Both choline and methionine occupy central roles in hepatic lipid metabolism. Both function as methyl donors and their metabolism is interrelated; choline has an additional specific role in neurotransmitter synthesis and cell membrane structure as phosphatidylcholine, and methionine has a specific role in protein and Cys synthesis (Figure 8). Methionine donates its methyl group to phosphatidylethanolamine after reacting with ATP, forming phosphatidylcholine (Figure 9). As mentioned above, phosphatidylcholine plays an important role in VLDL synthesis (for assembly and stability of the lipoprotein particle). Emmanuel and Kennelly (1984) found that 28% of radioactivity from L-[methyl-^{14}C]methionine was recovered in choline in lactating goats; indicating that choline biosynthesis is an important fate of methionine fed to ruminants.

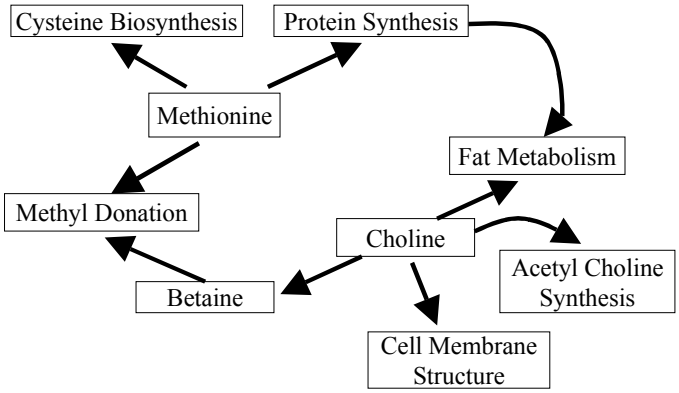

Figure 8. Potential interrelationships of methionine, betaine, and choline in liver metabolism of periparturient dairy cows.

Although researchers have speculated about the potential role of methionine in liver fatty acid metabolism in transition cows for more than thirty years, experimental evidence for this role is scarce. There also could be potential for involvement of 2-hydroxy-(4-methylthio)-butanoic acid (HMB), an analog of methionine, in metabolism of transition cows. Production responses in previous experiments to supplementation of HMB to diets designed to be deficient in methionine have been mixed (Rode et al., 1998; Johnson et al., 1999); therefore, we conducted and recently reported data from an experiment designed to determine whether production and metabolism of transition cows is sensitive to supply of HMB (Piepenbrink et al., 2001).

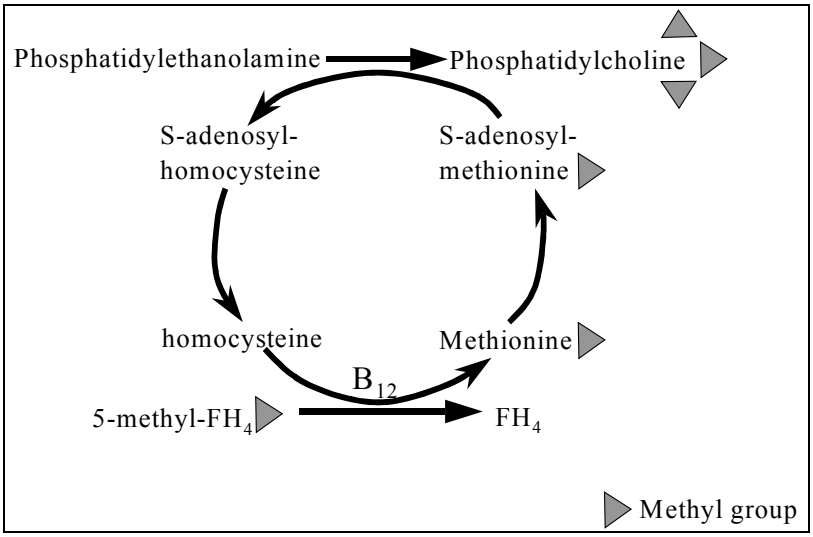

Figure 9. Synthesis of phosphatidylcholine utilizing the methyl groups of methionine and methionine synthesis from the methylation of homocysteine utilizing the methyl group of 5-methyl-tetrahydrofolate.

We formulated prepartum and postpartum basal diets to be deficient in methionine using ratio (Schwab and Rulquin) methods as benchmarks, and added two amounts of HMB (Alimet® Feed Supplement, Novus International, St. Louis, MO) to the basal diet (Table 4). to achieve a projected Lys to Met ratio of 3 and 2.7, respectively. In this study, the diet with the low dose of HMB was defined to provide the recommended levels of Lys and Met at a 3 to 1 ratio as described by Schwab (1996) and Rulquin and Verite (1993) for lactating dairy cows. The diet with the high dose of HMB was formulated to provide Met in excess of the

Table 4. Projected AA balance of the experimental diets (Piepenbrink et al., 2001)[1].

	Prepartum			Postpartum		
AA	Basal	+ HMB	++ HMB	Basal	+ HMB	++ HMB
Methionine						
% MP	2.01	2.34	2.70	1.86	2.36	2.63
Lysine						
% MP	7.36	7.33	7.31	7.22	7.19	7.17
Ratio Lys: Met	3.66	3.13	2.71	3.88	3.05	2.73

[1]Projected using CPM Dairy based upon feed analyses conducted during the experiment.

recommendations, reducing the Lys to Met ratio to 2.7. Treatments were initiated at 21 days before expected calving and continued through day 84 of lactation.

Differences in prepartum and postpartum dry matter intake among treatments were not significant (Table 5). Based upon actual mean dry matter intakes of cows during the experiment, average consumption of HMB was 14 and 30 grams per day for the two HMB treatments, respectively, during the prepartum period. Actual consumption of HMB during the postpartum period averaged 34 and 51 grams per day, respectively, for the two HMB treatments.

Cows fed the middle treatment (low level of HMB) produced significantly more milk (6.6 lbs per day) than cows fed either the control ration or the ration containing the high level of HMB (Table 6). Effects of treatment on milk composition (percentages of fat, protein, lactose, or total solids) were not significant; therefore, trends for increased yields of 3.5% fat-corrected milk and total solids, and a significant increase in lactose yield, by cows fed the low level of HMB reflect the increased milk yield by cows fed this treatment.

Table 5. Least squares means for dry matter intake (DMI) of cows fed increasing amounts of 2-hydroxy-4-(methylthio)-butanoic acid (HMB) during the transition period and early lactation.

	Treatment				Effect, P <		
Item	Control	+ HMB	++ HMB	SEM	TRT Linear	TRT Quad.	TRT x week
Prepartum DMI, lb/d	28.4	28.2	28.0	0.84	0.71	0.98	0.82
Postpartum DMI, lb/d	41.0	43.6	43.4	1.39	0.22	0.41	0.99

Table 6. Least squares means for yield of milk and composition and yield of milk components from cows fed increasing amounts of 2-hydroxy-4-(methylthio)-butanoic acid (HMB) during the transition period and early lactation.

	Treatment				Effect, P <		
Item	Control	+ HMB	++ HMB	SEM	TRT Linear	TRT Quad.	TRT x week
Milk, lb/d	92.6	99.2	92.6	2.9	0.99	0.05	0.13
Fat, %	4.20	4.00	4.07	0.13	0.46	0.36	0.80
Fat, lb/d	3.79	3.88	3.70	0.11	0.59	0.32	0.40
3.5% FCM, lb/d	101.4	105.8	100.1	2.6	0.70	0.11	0.28
CP, %	2.80	2.77	2.84	0.06	0.65	0.33	0.26
CP, lb/d	2.56	2.69	2.58	0.09	0.77	0.22	0.69
Lactose, %	4.70	4.69	4.73	0.05	0.62	0.69	0.76
Lactose, lb/d	4.34	4.65	4.39	0.13	0.86	0.05	0.19
Total solids, %	12.46	12.22	12.38	0.19	0.78	0.36	0.94
Total solids, lb/d	11.40	11.99	11.35	0.31	0.94	0.09	0.53

Blood was sampled from each cow every other day from the initiation of treatment until 30 days postpartum and analyzed for NEFA and BHBA. There were no significant effects of treatment on concentrations of either metabolite in plasma. A treatment by time interaction existed for concentrations of liver triglyceride on days 1 and 21 postcalving because the concentration was elevated for cows fed the + HMB treatment on day 21 postcalving; we believe that the increase is related to the increased milk yield by cows fed this treatment rather than a direct effect on liver fatty acid metabolism. In support of this interpretation, rates of use of [1-^{14}C]palmitate for fuel and accumulation as liver fat in vitro were not sensitive to supply of HMB.

CURRENT RESEARCH, AND IMPLICATIONS FOR THE DAIRY INDUSTRY

Currently, our laboratory is engaged in followup experiments to determine more specifically which pathways of fatty acid metabolism in liver are sensitive to supplies of choline, HMB, and methionine and other related compounds such as methionine and its analog. These data, together with the collective data from research conducted during the past several years worldwide, will continue to improve our understanding of the metabolic adaptations that must occur in liver if cows are to successfully transition to lactation. Data presented in this paper suggest that we can employ nutritional strategies to optimize liver fatty acid metabolism and in turn

improve metabolic health and performance of transition cows. Formulating dairy diets based upon ratios of Lys and Met during the transition period or supplementing diets with CLA appear to have potential for enhancing performance of cows during the transition period. These strategies will be increasingly deployed to the dairy industry in nutritional programs for transition cows in the future.

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