ADSA FOUNDATION SCHOLAR AWARD

Biology of Dairy Cows During the Transition Period: the Final Frontier?

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ABSTRACT

The transition period, from 3 wk before to 3 wk after parturition, is critically important to health, production, and profitability of dairy cows. Most health disorders occur during this time. Compared with other stages of the lactation cycle, relatively little is known about fundamental biological processes during the transition period. The regulation and coordination of lipid metabolism among adipose tissue, liver, gut, and mammary gland are key components of the adaptations to lactation. Lipid accumulation in liver may contribute to health disorders and decreased milk production. Knowledge of key control points in hepatic metabolism of long-chain fatty acids is lacking, as is an understanding of the metabolic effects of hormones, growth factors, and cytokines that mediate stress. Recent evidence indicates that supplemental fats or restricted intakes before parturition can induce a coordinated set of metabolic changes in metabolism of long-chain fatty acids, including peroxisomal β-oxidation, perhaps mediated by peroxisome proliferator-activated receptors. Estimates of the mixture of fuels constituting metabolizable energy in cows during the early postpartum period suggest that supply of amino acids and glucogenic compounds may be under proposed optima, whereas ketogenic and lipogenic compounds and long-chain fatty acids may be in excess. Because dietary fat does not suppress body lipid mobilization, during the early postpartum period supplemental fat may further imbalance the mixture of fuels and lead to decreased dry matter intake. Increased understanding of the biology of the transition period should decrease health problems and increase profitability of dairy cows.
(**Key words:** transition, liver, lipid metabolism, dietary fat)

Abbreviation key: CPT-1 = carnitine palmitoyltransferase-1, **FA** = fatty acids, **HDL** = high density lipoproteins, **ME** = metabolizable energy, **PDV** = portal-drained viscera, **PPAR** = peroxisome proliferator-activated receptors, **TG** = triglyceride, **VLDL** = very low density lipoproteins.

Received April 19, 1999.
Accepted June 10, 1999.

INTRODUCTION

An ancient Chinese curse states, in effect, "May you always live in interesting times." In this context, the transition period between late pregnancy and early lactation (also called the periparturient period) certainly is the most interesting stage of the lactation cycle. Although the length of time classified as the transition period has been defined differently by different authors, I define it as did Grummer (45) as the last 3 wk before parturition to 3 wk after parturition. Most infectious diseases and metabolic disorders occur during this time. Milk fever, ketosis, retained fetal membranes, metritis, and displaced abomasum primarily impact cows during the periparturient period. Immunosuppression during the periparturient period (72) leads to increased susceptibility to mastitis. Indeed, the incidence of environmental mastitis is greatest around parturition (99). Thus, the occurrence of health problems is centered disproportionately on this relatively short period, which certainly contributes to making this an "interesting" time for dairy producers. As stated by Goff and Horst (37), "The transition from the pregnant, nonlactating state to the nonpregnant, lactating state is too often a disastrous experience for the cow... The well-being and profitability of the cow could be greatly enhanced by understanding those factors that account for the high disease incidence in periparturient cows."

As a requirement for the ADSA Foundation Scholar award, the winner is asked to speak and write on "an issue of critical importance to the dairy industry." My contention is that improved understanding of this frontier of the biology, nutrition, and management of cows during the transition period will provide the largest gains in productivity and profitability during the next decade.

Nutrition and management of cows during the transition period has received tremendous interest in recent years. Several excellent reviews of aspects of this topic have been published recently (11, 37, 39, 45). Those reviews still represent the state of the art in those areas, and it is not my intent to repeat those efforts. Rather, I will focus on some aspects of the importance of the transition period, including why I refer to it as the "final frontier," then discuss some recent insights from our laboratory on metabolism during the transition period.

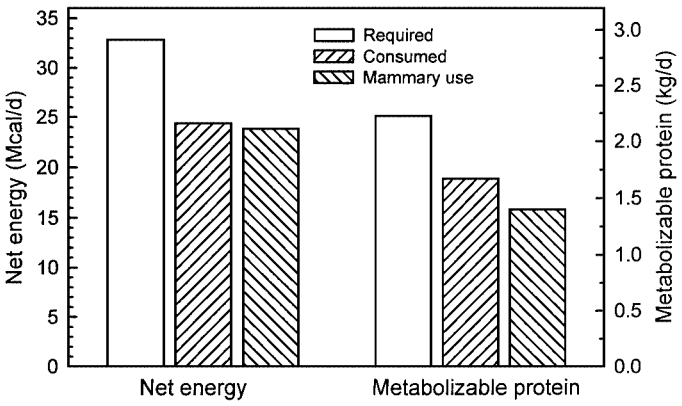

Figure 1. Calculations of amounts of NE_L and metabolizable protein required, consumed, and utilized by lactating mammary gland of healthy dairy cows at 4 d postpartum. Adapted from Bell (11).

A final objective is to highlight some challenges for the future to further our understanding of this critical period in the lactation cycle.

IMPORTANCE OF THE TRANSITION PERIOD

The success of the transition period effectively determines the profitability of the cow during that lactation. Nutritional or management limitations during this time may impede the ability of the cow to reach maximal milk production. The primary challenge faced by cows is a sudden and marked increase of nutrient requirements for milk production, at a time when DMI, and thus nutrient supply, lags far behind. This situation is exhibited clearly in data presented by Bell (11), which have been plotted in Figure 1. Requirements for NE_L and metabolizable protein by healthy cows at 4 d postpartum exceeded intakes by 26 and 25%, respectively. Furthermore, calculated utilization of NE_L and metabolizable protein by the mammary gland for milk production accounted for 97 and 83%, respectively, of intakes, leaving little to supply maintenance needs.

The constraints imposed by the deficient intakes, coupled with other stressors associated with parturition and adjustments to lactation, no doubt contribute to the high incidence of health disorders during the transition period. Survey data of disease incidence in transition cows vary widely, yet it is this variation itself that is perhaps so fascinating. Jordan and Fourdraine (57) reported data for disease incidence from a survey in 1991 of 61 of the highest producing dairy herds in the United States (Table 1). Although mean incidences of disorders were not surprising, the range of reported incidences is striking. For example, the mean incidence of milk fever was 7.2%, but the range was 0 to 44.1%. The implications of that range are intriguing. How could these farms achieve some of the highest production averages in the United States with incidences of disorders so high? On the other hand, how much greater would their milk production be if these disorders were decreased?

The occurrence of health disorders during the transition period results in lost milk production during the time of illness and often for the entire lactation. For example, Rajala-Schultz et al. (84) found that ketosis decreased milk yield for cows in parity 4 or greater by 535 kg during a 305-d lactation. Wallace et al. (106) studied the impact of health problems during the periparturient period on milk yield. Cows with any health disorder around calving produced 7.2 kg less milk per day during the first 20 d postpartum than did healthy cows. Cows with retained fetal membranes and subsequent metritis produced 8.2 kg less milk per day, and those with displaced abomasum and secondary ketosis produced 8.5 kg/d less, than cows with no health disorders. For cows with displaced abomasum and ketosis, the projected 305-d 2× mature equivalent milk yield was significantly lower (8573 kg) than that for healthy cows (9426 kg). Clearly, occurrences of periparturient diseases and disorders have lasting negative impacts on milk yield during that lactation, in addition to the cost of lost saleable milk during treatment for the disorder and costs of veterinary treatment. Extreme negative energy balance and extensive loss of body condition during the periparturient period also may impinge on subsequent reproductive success (100).

WHY THE "FINAL FRONTIER"?

According to Webster's Third New International Dictionary (107), a "frontier" is "an area (as of thought or investigation) that constitutes the most advanced, obscure, or unexploited field or line of inquiry with respect to a particular subject: the farthermost limits of knowledge or achievement," or "a new or relatively unexploited field that offers scope for large exploitative or developmental activity." In my opinion, understanding the biology of the transition period constitutes a major frontier under these definitions. The transition period

TABLE 1. Mean and range for incidence of selected periparturient health disorders in 61 herds of high producing dairy cows.[1]

Disorder	Mean (%)	Range (%)
Milk fever	7.2	0 to 44.1
Displaced abomasum	3.3	0 to 14
Ketosis	3.7	0 to 20
Retained fetal membranes	9.0	0 to 22.6
Metritis	12.8	0 to 66

[1]Adapted from Jordan and Fourdraine (57).

is very poorly understood in comparison with our knowledge of cows during and after peak lactation. Grummer (45) stated that "...there is a very small literature base to make conclusions on how to feed the transition cow."

Several factors contribute to this small knowledge base about the transition period. Historically, researchers have often avoided this period when conducting nutritional or management studies, instead focusing either on the dry period or on lactation after the first 2 to 3 wk postpartum. The transition period presents several challenges to the conduct of research. Perhaps the biggest challenge is that events happen quickly and physiological state changes rapidly, with most of the adaptations probably completed within about a 4-wk period from 2 wk before to 2 wk after calving. Measurements during this time are fraught with a high degree of variability, reflecting differences among individual cows in the success of adaptation to lactation. Indeed, coefficients of variation for DMI during the 1st wk postpartum are in the range of 30 to 40%, whereas for DMI after peak lactation coefficients of variation typically are 6 to 10%. The high incidence of health problems during this time contributes to the variation in DMI, milk yield, and responses to imposed treatments. Lack of suitable covariate measurements makes analysis more difficult and requires larger numbers of cows to detect differences statistically. Large numbers of cows are required to assess impacts of nutrition and management on the incidences of health disorders and reproductive success. Finally, treatments may be confounded by the changes in facilities and environments that the cows may be moved through during the transition period.

Because of the relative lack of research, there are numerous gaps in fundamental knowledge of the biology of cows during the transition period. Some examples are given here to stimulate creative researchers to seek answers. Why do vastly different nutrition and management programs produce similarly good, or similarly poor, transition success? What are the underlying mechanisms that lead to displaced abomasum, ketosis, retained fetal membranes, and milk fever? What controls DMI during the transition period? How do the limited DMI and the gastrointestinal hypertrophy during this period impact nutrient supply (e.g., production of VFA and microbial protein)? How does the immune system impact normal (and abnormal) metabolism during the transition period? What are the mechanisms involved in the immunosuppression associated with the periparturient period? How much genetic variation is present for differences in transition success? Does the current increase in inbreeding in the Holstein breed result in greater susceptibility to periparturient disease? How do nutrition and management during the dry period and transition period impact subsequent reproductive success? While this is not an exhaustive list, and the relative state of knowledge among these areas varies, these examples are meant to highlight the potential interactions of nearly all fields of dairy cattle biology on success and implications of the transition period.

Currently, so-called fresh-cow medicine programs are being widely implemented in the veterinary community, as part of production medicine practices. Such programs include close monitoring and aggressive treatment for any signs of disease during the first few days after parturition, and may include varying degrees of prophylactic treatment with glucose precursors, calcium sources, and antibiotics. These programs often are quite successful in decreasing the incidence of health disorders and allowing cows to obtain earlier peaks of DMI and milk production. However, they also add cost to producers. Is there a better way? Would increased understanding of the fundamental biological processes of the adaptation to lactation make us more able to design nutritional and management programs for transition success?

LIPID METABOLISM DURING THE TRANSITION PERIOD

A key area of the biology of transition cows relates to lipid metabolism. Excessive lipid mobilization from adipose tissue is linked with greater incidences of periparturient health problems. Fatty livers were shown to occur in ketotic cows nearly a half-century ago (91). Subsequently, hepatic fat accumulation also was noted in "clinically normal" cows during early lactation (34). Roberts et al. (89) described a "fat mobilisation syndrome" in early lactation, in which cows mobilized body lipids from adipose tissue and deposited lipids in the liver, muscle, and other tissues. More recently, Dyk et al. (30) found that elevated NEFA concentrations during the last 7 d before calving were associated with greater incidences of ketosis, displaced abomasum, and retained fetal membranes but not of milk fever. Understanding metabolism of NEFA by the liver is a critical component of understanding the biology of the transition cow.

Extreme rates of lipid mobilization lead to increased uptake of NEFA by liver and increased triglyceride (**TG**) accumulation (Figure 2). If this lipid infiltration becomes severe, the syndrome of hepatic lipidosis or fatty liver may result, which can lead to prolonged recovery for other disorders, increased incidence of health problems, and development of "downer cows" that may die (47). Increased lipid accumulation and decreased glycogen in the liver were associated with an increased

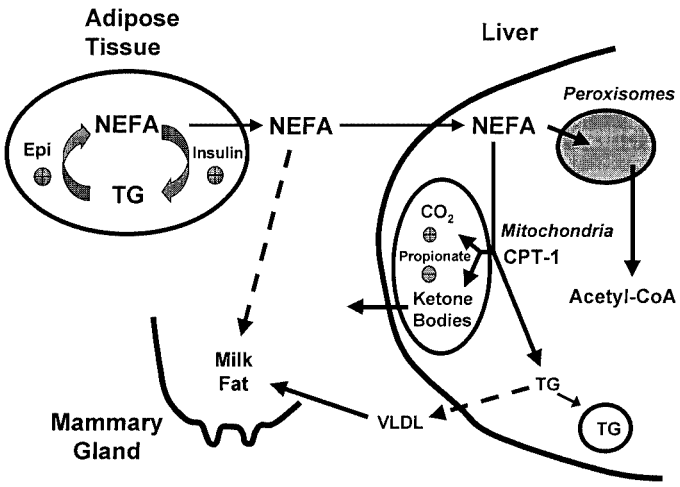

Figure 2. Schematic representation of relationships among lipid metabolism in adipose tissue, liver, and mammary gland. Plus signs (+) indicate stimulatory effects, minus signs (–) indicate inhibitory effects. Dashed lines indicate processes that occur at low rates or only during certain physiological states. Abbreviations: epi = epinephrine, TG = triglyceride, VLDL = very-low-density lipoproteins, CPT-1 = carnitine palmitoyltransferase 1.

susceptibility to induction of ketosis (24). The exact nature of the impact of lipid infiltration on normal hepatic functions is not clear. West (108) found significant positive correlations between the degree of fatty infiltration in cows with ketosis or fat cow syndrome and concentrations of total bilirubin (r = 0.62) and total bile acids (r = 0.61) in plasma, and negative correlations with plasma glucose (r = –0.54), plasma urea (r = –0.57), and serum albumin (r = –0.71). Other research, however, showed no relationship between the degree of lipid accumulation and liver function in cows with fatty liver subsequent to displaced abomasum (85). Recent evidence indicates that fat infiltration per se does not affect gluconeogenesis by bovine hepatocytes (101). However, TG accumulation in hepatocytes decreased capacity for urea synthesis (101) and ammonia decreases the ability of hepatocytes to synthesize glucose from propionate (79); therefore, TG accumulation may indirectly inhibit glucose synthesis in cows (101). Rates of synthesis of total protein and albumin were not affected by TG accumulation in bovine hepatocytes, but insulin clearance rates were decreased (102).

The general scheme for metabolism of NEFA in liver is shown in Figure 2. Regulation of NEFA metabolism in adipose tissue (73) and liver (10, 32, 44, 50, 112) has been reviewed during the last decade. Major control points in hepatic metabolism of NEFA are in 1) delivery of NEFA to the liver, and 2) uptake of NEFA into mitochondria, which is regulated by activity of carnitine palmitoyltransferase I (**CPT-1**; EC 2.3.1.21). Additional metabolic control may be exerted at other locations in lipid metabolic pathways, including the regulatory enzyme of mitochondrial ketogenesis (32), 3-hydroxy-3-methylglutaryl CoA synthase (EC 4.1.3.5); the regulated steps within the esterification pathway (49, 103, 104), including glycerol-3-phosphate acyltransferase (EC 2.3.1.15/51), phosphatidate phosphohydrolase (EC 3.1.3.4), and diacylglyerol acyltransferase (EC 2.3.1.20); the partitioning of newly synthesized TG between secretion and storage (44); and the inherently low rate of synthesis and export of very low density lipoprotein (**VLDL**) in ruminant liver (9, 10, 32, 44).

Factors regulating the relative flux of NEFA between oxidation and esterification are not well understood in dairy cows. Recent evidence that fatty liver has largely developed by the day after parturition (44) and that fatty liver precedes an induced ketosis (105) suggests that the liver is prone to increased NEFA esterification and TG deposition around calving. Indeed, we recently demonstrated that esterification of palmitate by liver slices was markedly increased at 1 d after calving compared with 21 d before or 21 d after calving (42). Evidence in rats indicates that insulin enhances activities of the enzymes of TG formation in liver (113) but whether the same situation occurs in periparturient dairy cows is not known. Cadórniga-Valiño et al. (18) found that insulin increased the proportion of oleate uptake converted to cellular TG in cultured hepatocytes from preruminant calves. Such an effect of insulin could help to explain the greater incidence of fatty liver development in cows that are overfed during the dry period. However, Van Den Top et al. (103) found no evidence for enhanced enzymatic capability for TG synthesis in liver of cows that were overfed during the dry period compared with control cows.

In vitro experiments have consistently demonstrated that hepatic oxidation of NEFA is decreased by propionate (4, 25, 26, 54, 70), although the effect is less marked when propionate is present at near-physiologic concentrations (C. J. Ottemann-Abbamonte and J. K. Drackley, 1998, unpublished data). Propionate decreases ketogenesis at least in part by a mechanism unrelated to CPT-1 (26). Other potential mechanisms for the anti-ketogenic effects of propionate have been discussed by Emery et al. (32) and Grummer (44). Acetate (25, 55), insulin, glucose, and other glucogenic compounds (25, 54, 55, 70) also have been shown to decrease oxidation of long-chain fatty acids (**FA**). A possible exception is pyruvate and its related compounds such as lactate or alanine, which have been shown to either not affect oxidation or to increase oxidation (4, 25, 70). Acetoacetate decreased oxidation of palmitate to both CO_2 and acid-soluble products in bovine liver slices (25). In contrast, β-hydroxybutyrate decreased palmitate oxidation by bovine liver slices in the absence of L-carni-

tine addition to the incubation medium but increased oxidation in the presence of added carnitine (25). The effects of acetoacetate could be a mechanism by which high concentrations of ketone bodies control their own production during ketogenic states.

Despite the probable central role of CPT-1 in determining flux of NEFA within the ruminant liver, surprisingly little is known about its expression and regulation, especially in the transition cow. Activity of CPT-1 was greater at d 30 of lactation than at 60, 90, or 180 d of lactation (2). Activity of CPT-1 in ruminant liver was inhibited by malonyl-CoA (16, 59, 86) and methylmalonyl-CoA (16, 59) in mitochondria isolated from bovine or ovine liver. Inhibition by methylmalonyl-CoA may be a mechanism to link supply of propionate from ruminal fermentation with the need for NEFA oxidation (112). Concentrations of malonyl-CoA in ruminant liver have been reported to be similar to those measured in rat liver and to change predictably with nutritional state (16). The concentration of malonyl-CoA is regulated by activity of acetyl-CoA carboxylase (EC 6.4.1.2), which is active during well-fed conditions characterized by high insulin-to-glucagon ratios and inactive during insulin-deficient states (113). In rats, at least two isoforms of acetyl-CoA carboxylase are present. The α-form predominates in synthesis of FA, whereas the β-form is found in nonlipogenic tissues such as skeletal and heart muscle and serves to regulate FA oxidation (58). Whether the isoform present in ruminant liver, a nonlipogenic tissue, resembles the rodent β-form has not been investigated.

Recent experiments with laboratory rodents have demonstrated that, in addition to changes in expression of CPT-1 and changes in concentrations of malonyl-CoA, the sensitivity of CPT-1 to malonyl-CoA inhibition also is regulated according to physiological state. During situations of low circulating insulin or insulin resistance, CPT-1 is less sensitive to inhibition by malonyl-CoA (113). The net result of these changes in rats is that ketogenic states are characterized by increased expression of CPT-1, decreased intracellular concentration of malonyl-CoA, and decreased sensitivity of CPT-1 to inhibitory effects of malonyl-CoA. Inhibition constants for CPT-1 have not been determined in dairy cows relative to stage of lactation, energy balance, or development of ketosis. Current research in our laboratory has the objective of determining how dietary management during the dry period and transition period affects the expression and activity of CPT-1 and acetyl-CoA carboxylase.

Common management recommendations for transition cows are to provide as "stress-free" an environment as possible. Stressors increase release of NEFA from adipose tissue, but the effects on hepatic responses are less well defined. Herdt et al. (48) found that fatty liver was more severe after surgery to correct displaced abomasum than in cows that were starved at the same stage of lactation. Thus, factors in addition to feed deprivation contribute to enhanced formation of TG in liver. One likely candidate group of compounds is the cytokines. Compounds such as tumor-necrosis factor-α are known to increase esterification and decrease oxidation of FA in liver of rodents (56). Metabolic responses to the many physiological mediators of stress have not been characterized in transition cows. This field should be a productive area of study in efforts to optimize transition success.

Although catecholamines provide the primary stimulus for increased mobilization of NEFA from adipose tissue, effects of catecholamines on metabolism of NEFA by the liver have not been investigated in ruminants. Ruminant liver is sensitive to actions of both α and β adrenergic agonists (33). We have recently found that both epinephrine and norepinephrine increased esterification of palmitate by ovine hepatocytes, but had only small effects on palmitate oxidation (78).

An alternate pathway for hepatic oxidation of NEFA is present in peroxisomes, which are subcellular organelles present in most organs of the body (97). The oxidative pathway in peroxisomes is similar to that in mitochondria, with key exceptions. First, the initial oxidation step is catalyzed by an oxidase (acyl-CoA oxidase; EC 1.3.99.3), which results in production of hydrogen peroxide rather than reduced NAD. This difference results in capture of less energy in reduced cofactors and more heat release during peroxisomal β-oxidation than in mitochondrial β-oxidation. Second, peroxisomes do not contain a respiratory chain linked to ATP formation. Consequently, peroxisomal β-oxidation is not subject to control by energy demands of the cell. These characteristics serve to make peroxisomal β-oxidation well suited to partially oxidize FA and xenobiotic compounds that are poor substrates for mitochondrial enzymes. Peroxisomal β-oxidation may play a role as an "overflow" pathway to oxidize FA during extensive NEFA mobilization. In laboratory rodents, peroxisomal β-oxidation is induced by dietary fat, starvation, uncontrolled diabetes, and numerous compounds known as peroxisomal proliferators, with the best known being clofibrate (97).

The presence of peroxisomal β-oxidation in liver of ruminants was suggested by observations that substantial β-oxidation of NEFA occurred in the presence of tetradecylglycidic acid, an inhibitor of CPT-1, in bovine liver slices (26) and isolated caprine liver cells (4). Subsequent research in our laboratory (42) demonstrated substantial activity of peroxisomal β-oxidation in homogenates of bovine liver. The relative contribution of

peroxisomal β-oxidation to the first cycle of total palmitate oxidation was 50% for bovine liver but only 26% for liver from retired breeder rats. Peroxisomal β-oxidation in cows past peak lactation was not affected by high or low concentrate diets or by the addition of fat to the diet (41). However, peroxisomal β-oxidation was increased by feeding a high-fat diet to cows during the dry period (42; discussed in next section), suggesting that this pathway may be inducible in dairy cows and that it might be important during the transition period.

The role of organ systems other than the liver and mammary gland in utilization of NEFA has been relatively ignored in the transition cow. Ruminants in general do not oxidize NEFA as efficiently as do nonruminants (80). We recently have shown that in vitro palmitate oxidation was lower in skeletal muscle preparations from dairy cows than in those from rats (77). Relative to rat muscle, oxidation of NEFA by bovine muscle was less than would be expected merely on the basis of lower metabolic rate in cows. In contrast, cow muscle oxidized acetate at high rates (77).

Research has demonstrated a strong relationship between how much cows eat shortly after parturition and the incidence of metabolic problems. For example, Zamet et al. (111) found that DMI for cows that experienced health problems were 18% lower prepartum and 20% lower postpartum than for healthy cows. Lean et al. (66) reported that cows that developed clinical ketosis had lower DMI during the first 3 wk postpartum than either ketonemic or nonketotic cows. In the study by Wallace et al. (106), cows with any health disorder around parturition had decreased DMI during the first 20 d postpartum (13.9 vs. 17.8 kg/d). While these associations do not prove cause and effect, in all the cited examples, DMI was lower for some period before the health disorders developed. One metabolic connection between DMI and incidence of metabolic disorders may be through propionate supply. Propionate stimulates insulin secretion, which suppresses NEFA mobilization. As discussed earlier, propionate is antiketogenic in the liver. Propionate supply also is key for glucose production, which in turn would modulate energy balance and favor insulin release.

We have recently used this relationship between peripartal DMI and disease incidence to develop a simple model of ketosis (5). Veterinarians and nutritionists in the field consistently report that the greatest incidence of ketosis in US herds fed TMR is during the first 2 wk postpartum, in contrast to earlier findings in component-fed herds in which ketosis incidence generally was greatest between wk 2 and 7 postpartum (6). While it has long been known that starvation induces ketosis in early lactation (7) but not in later lactation or in nonlactating cows (8), our hypothesis was that a limitation in DMI during the 1st wk postpartum would cause ketosis. Otherwise healthy cows were fed for ad libitum DMI during the first 4 d postpartum. On d 5, feed offered was restricted to 50 or 25% of ad libitum intake for up to 7 d. Clinical ketosis was diagnosed in 8 of 10 feed-restricted cows, with no difference due to severity of feed restriction. The remaining 2 cows were highly ketonemic. None of the 5 control (ad libitum-fed) cows became ketonemic. Restricting DMI by 25% beginning at 14 d postpartum (28) or by as much as 50% at 6 to 7 wk postpartum (22) was ineffective in inducing ketosis. These results demonstrate that susceptibility to ketosis is increased by some metabolic factor or factors related to DMI during the very early postpartal period. Such a model should be useful in understanding adaptations in NEFA metabolism in transition cows.

EFFECTS OF DIETARY FAT ON LIPID METABOLISM IN TRANSITION COWS

Use of supplemental fats and oils in diets for dairy cows has become a standard practice. Extensive research has been conducted to determine the effects of supplemental fats on milk yield and composition, intake, and digestion. A much smaller body of research is available concerning the effects of dietary fats on postabsorptive metabolism in dairy cows (44, 46, 80). These issues assume practical as well as academic importance; for example, concern often is expressed about whether dietary fat increases the likelihood of fatty liver development or decreased liver function. Dietary fat results in widespread metabolic changes in rodents, including increased peroxisomal and mitochondrial β-oxidation of FA (64, 71), decreased esterification of FA (71), altered profiles and clearance of plasma lipoproteins (65), induction of xenobiotic metabolizing enzymes (110), and altered responsiveness to hormonal signals (21). Parallel changes in dairy cows could be important adaptations to use of dietary fat. Furthermore, because many of these changes in lipid metabolism induced by dietary fat also occur during starvation or negative energy balance in rodents, they might also be important adaptations during the transition period in dairy cows.

Our research group has undertaken studies to determine the effects of dietary fat on hepatic metabolism in dairy cows. Grum et al. (41) fed four diets in a Latin square design to cows past peak lactation. Diets were control (55% forage) or high grain (30% forage), both without or with supplemental fat (from 10% whole soybeans and 3% prilled saturated FA). Calculated content of NE_L was 1.6, 1.7, 1.7, and 1.8 Mcal/kg of DM for control, control plus fat, high grain without fat, and high grain plus fat, respectively. Total and peroxisomal β-oxidation in liver homogenates were unaffected by

diet. Liver glycogen was increased by the high grain diets, but liver lipid content was not affected. Total metabolism of palmitate (oxidation plus esterification) by liver slices was increased by either high grain or supplemental fat, with the means following the pattern of energy density of the diets. Greater in vitro capacity to metabolize palmitate indicates that dietary composition affected enzymatic capacities of liver. Total oxidation of palmitate by liver slices tended to be greater when diets contained supplemental fat. Energy intake was greatest when cows were fed either of the diets containing 1.7 Mcal/kg, and decreased for the highest energy diet. These findings may provide support for the notion that increased FA oxidation in liver may help regulate DMI as described by Emery et al. (32).

Because potential changes in hepatic lipid metabolism would be expected to be more pronounced during the periparturient period, Grum et al. (42) conducted a study with the following objectives: 1) to determine the role of peroxisomal β-oxidation in dairy cows during the periparturient period, 2) to determine whether dietary fat could be used to restore body condition to cows that were thinner than desired going into the dry period, 3) to determine the effects of dietary fat on hepatic NEFA metabolism, and 4) to determine whether dietary fat contributes to development of fatty liver around parturition. Holstein cows with body condition scores of ≤3.5 (5-point scale; 1 = thin to 5 = obese) at dry-off were assigned to one of three diets during the dry period: a high-forage control diet (NE_L = 1.27 Mcal/kg), a high-forage diet plus 6.5% choice white grease (NE_L = 1.44 Mcal/kg), or a high-grain diet (NE_L = 1.44 Mcal/kg). Cows were fed for ad libitum intake throughout the dry period until about 1 wk before expected calving, when they were switched to a diet of 2/3 of the dry cow forage (oat hay) and 1/3 of the lactation TMR. After calving, all cows were fed the same lactation diet. At 1 d postpartum, cows that were fed the high-fat diet prepartum had little TG accumulation in the liver (1.4% of wet weight) compared with those fed control (7.3%) or high grain diets (5.9%). The lower liver lipid concentrations were accompanied by less marked increases of NEFA around parturition, little increase in the capacity of liver slices to esterify palmitate, and increased peroxisomal β-oxidation in liver homogenates. These changes indicate that the high-fat diet fed throughout the dry period resulted in a coordinated set of adaptations in lipid metabolism that culminated in less hepatic TG accumulation at parturition. However, DMI was decreased by the high-fat diet, which made it difficult to ascribe the metabolic changes to dietary fat content rather than to decreased nutrient intake. The effect of the high-fat diet was specific to the periparturient period because a high-fat diet fed from d 21 to 300 of lactation did not result in increased peroxisomal β-oxidation (40).

In a follow-up study, Douglas et al. (23) fed isocaloric diets without or with supplemental fat (4% of DM), either at ad libitum intake [averaging about 120% of NRC (75) requirements for NE_L] or restricted to provide only 80% of NE_L requirements during the dry period. The degree of feed restriction was set to correspond with the decreased nutrient intake of the fat-supplemented cows in the study by Grum et al. (42). Cows fed either diet at restricted intake had less accumulation of lipid in the liver 1 d after parturition; the effects of dietary fat were smaller but additive to those of intake, resulting in lower TG concentrations at 1 d postpartum for cows fed the high-fat diets. Cows fed at restricted intake also had greater DMI postpartum and tended to produce more milk.

Mechanisms for the coordinated set of adaptive changes induced by dietary fat or nutrient restriction are unclear, but evidence from studies with rodents provides a plausible hypothesis. Most of the changes in enzyme activities induced by high-fat diets or starvation in laboratory rodents are mediated by interaction of FA or their metabolites with specific nuclear receptors called peroxisome proliferator-activated receptors (**PPAR**). The PPAR were first identified in mouse liver by Isseman and Green (53) and types have now been cloned from *Xenopus*, rat, hamster, guinea pig, and human tissues (94). These novel receptors are members of the nuclear receptor superfamily and consist of at least three types [α, β (or δ), and γ] that vary in tissue distribution. In rodents, PPARα is predominantly found in liver, heart, kidney, and brown adipose tissue, with smaller amounts in skeletal muscle, small intestine, thymus, and testis; at least one of the isoforms of PPARγ is intimately involved in adipose tissue biogenesis. Activation of PPAR by FA, eicosanoids, or xenobiotics leads to binding of the PPAR to specific response areas of target genes, leading to activation or repression of gene expression (94). Peroxisome proliferator response elements have been identified in the promoter regions of a number of genes encoding proteins found in peroxisomes, mitochondria, microsomes, and cytosol that are involved in lipid metabolism. In particular, activation of PPARα leads to a coordinated induction of enzymes involved in plasma transport, intracellular trafficking, and metabolism of FA. In rodents, stresses such as immobilization lead to increased expression of PPARα and subsequent increases of target gene expression (67), as do both starvation and diabetes (61).

Consequently, dietary fat or elevated NEFA from decreased nutrient intake in the studies of Grum et al. (41) and Douglas et al. (23) may have increased expression and action of PPAR, leading to increased hepatic

oxidation and decreased esterification of FA observed in liver tissue. Both starvation and increased dietary fat intake lead to increases of acyl-CoA concentrations in rat liver (76). The mechanisms whereby dietary fat would lead to increased concentrations of FA or fatty acyl-CoA in liver, followed by increased expression and action of PPAR, have not been defined clearly because the extent to which dietary FA enter the liver has not been determined, especially in ruminants. After absorption into small intestinal epithelial cells, dietary FA are reesterified and the resulting TG packaged into lipoproteins. The TG-rich lipoproteins (chylomicron and VLDL) mostly enter the lymphatic system so dietary FA reach peripheral tissues before the liver (Figure 3). Clearance of remnant lipoprotein particles may occur by the liver.

At least three potential mechanisms can be proposed that would explain possible alterations in liver metabolism in cows fed supplemental fats: 1) Dietary fat results in increased NEFA concentration in plasma, with resulting increases in NEFA uptake by liver. 2) Increased uptake of lipoprotein particles increases uptake of FA by liver. 3) Consumption of dietary fat results in changes in hormonal profiles, receptor expression or sensitivity, or signal transduction mechanisms that affect metabolism in liver.

Regarding the first possibility, supplemental dietary fat does increase the concentration of NEFA in plasma of dairy cows (19, 46). Data for NEFA concentrations from seven studies (20, 27, 31, 81, 90, 93, 96) in which graded amounts of fat were fed to lactating dairy cows are plotted in Figure 4. From the regression relationship, a 1 kg/d increase of FA intake would result in an increase in NEFA concentration of only 81 μM. This result is similar to the average increase (41 ± 90 μM) found by Chilliard (19) for 50 treatment comparisons. The magnitude of this increase is much less than typical changes observed during the transition period, where NEFA concentrations may increase by 1 mM or more (44). Consequently, it is difficult to ascribe the marked changes in metabolism observed in our studies to the modest increase of NEFA expected from dietary fat.

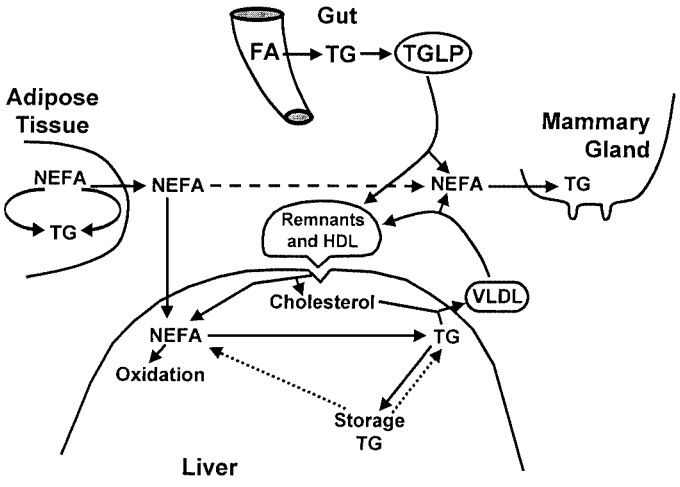

Figure 3. Schematic representation of metabolism of NEFA mobilized from adipose tissue and dietary fatty acids (FA) absorbed from the gut. After absorption, dietary FA are packaged into triglyceride (TG)-rich lipoproteins (TGLP), which deliver dietary FA to peripheral tissues. Dietary FA result in elevation of the concentration of NEFA as a consequence of lipoprotein lipase action in peripheral tissues. Remnant lipoproteins and high-density lipoproteins (HDL) are cleared by the liver, thereby delivering FA to the liver.

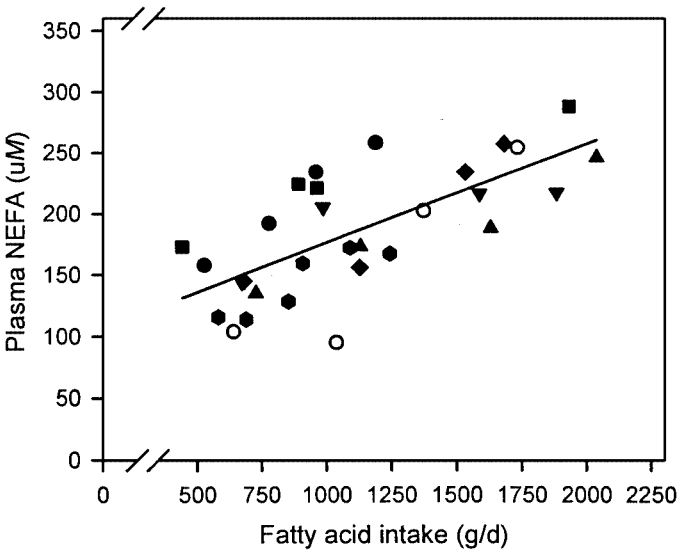

Figure 4. Relationship between amounts of dietary fatty acids consumed (X, g/d) and NEFA concentration in plasma (Y, μM). The solid line shows the regression Y = 95.2 + 0.0806X (r^2 = 0.506). Data are from studies (20, 27, 31, 81, 90, 93, 96) in which multiple amounts of fat were fed. Different symbols represent different intakes of dietary fat from the same study.

Hepatic uptake of FA from lipoprotein particles may be sufficient to signal changes in metabolism. Bergman et al. (12) showed that about 10% of chylomicron TG was removed by the liver of sheep. Recent studies by Durand et al. (29) and Leplaix-Charlat et al. (69) demonstrated disappearance of VLDL across the liver of periparturient cows and milk-fed calves, respectively. Ruminant liver contains essentially no lipoprotein lipase (EC 3.1.1.34) or hepatic TG lipase (EC 3.1.1.3) to allow use of plasma TG (32). However, Bauchart et al. (10) have speculated that extrahepatic lipoprotein lipase present in plasma could be sufficient to catalyze TG hydrolysis in hepatic sinusoids. Although little is known about metabolism and clearance of remnant lipoproteins in ruminants, liver is believed to be the major site of uptake of the remnant TG-rich lipoproteins, most likely through endocytosis (9, 32). Significant he-

patic uptake of relatively lipid-rich high-density lipoproteins (**HDL**) also has been demonstrated in calves (69). Hepatic uptake of VLDL, VLDL remnants, or HDL by cows fed fat could deliver appreciable quantities of FA to the liver that in turn could stimulate enzymes for their metabolism via PPAR.

Alterations in hormonal profiles from feeding fat during the periparturient period could be another mechanism resulting in changes in hepatic lipid metabolism. Changes in hormone concentrations of cows fed the fat-supplemented diet prepartum in the study by Grum et al. (42) generally were consistent with decreased energy balance. Alterations in insulin and glucagon sensitivity and responsiveness have been implicated in the etiology of ketosis (50). Low insulin enhances, whereas high insulin suppresses, peroxisomal β-oxidation (109). Dietary fat decreases plasma insulin (20); insulin was decreased prepartum for cows fed the fat-supplemented diet in the study of Grum et al. (42). Glucocorticoids increase expression of PPARα in rat hepatocytes (68). While cortisol was not measured in our studies, its concentration increases markedly around the time of calving (38). The receptor for the thyroid hormone, triiodothyronine, interacts with PPAR in regulating genes with peroxisome proliferator response elements (52). Prepartal concentrations of triiodothyronine were numerically lower in cows fed fat prepartum, although the ratio of triiodothyronine to thyroxine was increased (42).

In addition to changes in circulating hormone concentrations, dietary fat also could induce alterations in hormonal responsiveness or signal transduction mechanisms. For example, altered membrane fluidity caused by supplemental fat or mobilized NEFA could affect hormone receptor responsiveness as observed in rats (15, 21). We recently have shown that the type of FA fed or abomasally infused to periparturient cows alters membrane FA composition (J. Rehage, G. N. Douglas, and J. K. Drackley, 1999, unpublished data), which in turn could affect membrane fluidity and the function of integral membrane proteins.

In other studies in which fat was supplemented to dairy cows, liver TG has been unchanged or increased. Bertics and Grummer (13) used a feed restriction model in nonlactating pregnant cows that were 51 d before expected calving. Liver TG content was increased during short-term (10 d) supplementation of supplemental fat to feed-restricted cows. Skaar et al. (98) reported that dietary fat supplementation beginning 17 d before expected calving did not significantly affect liver TG at 1 d postpartum, although means were slightly higher for fat-supplemented cows. Differences between these results and those of our group (23, 42) may be related to the duration of fat supplementation. If supplemental fat alters periparturient metabolism through PPAR-mediated induction of lipid-metabolizing enzymes, it is possible that a longer supplementation period than was provided in the Wisconsin studies (13, 98) is necessary. Another factor that has not been considered is whether the profile of FA absorbed from the intestine may impact FA metabolism in the liver. In calves, milk replacer supplemented with soybean oil led to accumulation of TG in the liver, whereas tallow supplementation did not (69).

Whether these alterations in peripartal hepatic metabolism are beneficial to milk production or health remains to be determined. Milk production, postpartal DMI, and incidence of health disorders were not affected significantly by prepartum diet in the study by Grum et al. (42) but cow numbers were small (n = 10). Other studies in which fat was supplemented during the last 3 wk prepartum have shown no improvements in milk production (3, 92, 98). On the other hand, Holtenius et al. (51) found that increasing the amount of full-fat rapeseed before parturition had positive effects on health and postpartum performance.

Another aspect of dietary fat during the transition concerns its use in the postpartum diet. Kronfeld (63) proposed that supplemental fat would be beneficial in preventing ketosis and improving lactational efficiency by suppressing mobilization of NEFA from adipose tissue, which would result in less ketogenesis in the liver. However, research generally has not supported use of supplemental fat in the postpartum transition diet. Grummer (45) reviewed several studies in which fat supplemented in the early postpartum diet resulted in a delayed response of milk production to the supplemental fat. Two theories to explain this phenomenon are 1) a negative feedback on DMI from excessive FA in the mixture of available fuels, possibly mediated by increased NEFA oxidation in the liver (32, 80), and 2) insufficient absorbable AA or other nutrients needed for efficient metabolism of the dietary and endogenous FA (82). Both of these theories are related to the concept of an imbalanced mixture of fuels constituting metabolizable energy (**ME**).

Central to the argument that dietary fat should be beneficial to early lactation cows is that dietary fat will suppress NEFA mobilization. However, evidence does not support a large decrease in lipid mobilization when fat is supplemented to the diet. Bines et al. (14) noted that increasing dietary lipid supply did not decrease body energy mobilization. Gagliostro and Chilliard (35) observed that duodenal infusion of rapeseed oil to cows during the periparturient period increased calculated energy balance but did not decrease losses of empty BW, condition score, subcutaneous adipocyte diameter, or estimated body lipids. Furthermore, in vitro lipolytic

rates in subcutaneous and perirenal adipose tissue were not suppressed by oil infusion during early lactation (36). Chilliard (19) summarized results of 11 experiments in which cows during early lactation were fed fat-supplemented diets. Energy balance was improved by an average of 1.1 Mcal/d, but BW change (–65 g/d) was not decreased. Komaragiri et al. (60) found that cows fed a diet with 3% added fat mobilized similar amounts of body lipid between –2 and 5 wk postpartum as did control cows, although greater initial body lipid stores in control cows complicated interpretation. Taken together, these findings indicate that supplemental dietary fat does not suppress body fat mobilization and subsequently would increase the amount of long-chain FA available for metabolism in the body. Body composition data derived by chemical analysis after slaughter are needed to better define the effects of supplemental fat on periparturient cows.

The hypothesis that a mixture of absorbed supplemental fat and mobilized NEFA results in decreased DMI because of a "nutrient imbalance satiety factor" (80) is particularly appealing as an explanation for the lack of improvement in milk production in the early postpartal cow. Although Kronfeld (62) presented the first detailed analysis and suggestion of the appropriate mixture of fuels to optimize milk production efficiency, the theoretical basis for an appropriate balance of lipogenic and glucogenic nutrients was not a new concept (1). A rigorous test of this hypothesis will require quantification of the mixture of nutrients actually available to the transition cow. To date, such data are not available.

A crude initial estimate of the composition of fuels available to the early postpartum cow can be made by extrapolation of data from Reynolds et al. (87, 88). In that study, four Holstein cows were fitted with multiple catheters to allow calculation of nutrient flux across the portal drained viscera (**PDV**) and liver. Measurements were made at 4 and 8 wk postpartum. At 4 wk postpartum, milk yield averaged 31.9 kg/d and mean DMI was 14.5 kg/d (2.3% of BW). Mean concentrations of glucose, β-hydroxybutyrate, and NEFA were 54.7 mg/dl, 9.6 mg/dl, and 328 μM, respectively. Cows were fed a diet containing (DM basis) 60.0% corn silage, 20.2% ground barley, 8.0% linseed meal, 9.6% corn gluten meal, and 2.2% minerals and vitamins. Total dietary CP was 15.6%, and nonfiber carbohydrate was estimated to be 36.9%.

Net PDV flux of components of ME (88) is shown in Table 2. This measurement underestimates total ME supply to the animal by the amount of nutrients used by the PDV tissues themselves and by the amount of dietary nutrients absorbed into the lymphatic system (e.g., dietary FA); during times of negative energy balance adipose tissue mobilization also contributes fuels (e.g., NEFA) that would provide ME to tissues. Although the mixture of fuels used by PDV tissues has not been defined accurately, total fuel use was calculated from respiratory gas exchange across PDV (88; Table 2). A somewhat arbitrary mixture of fuels was assumed to supply energy for PDV tissues; AA was assumed to supply about 30% of energy needs (95), and the remaining energy was divided between glucogenic compounds (18%) and ketogenic compounds (52%) on the basis of the respiratory quotient across PDV (0.77 for PDV at 4 wk; 88). Summation of energy availability from PDV net flux and oxygen use by PDV results in a total of 30.8 Mcal of ME. Assuming that the FA content of the diet was 3.0% and that those FA were 70% digestible, dietary FA may have supplied another 3.4 Mcal, for a total dietary ME supply of 34.2 Mcal. Measured ME intake in this study was 39.6 Mcal/d (88). Potential dietary sources of ME not accounted for included pyruvate, formate, acetoacetate, glycerol, ethanol, nucleic acids, and peptides (88); underestimated digestible FA supply also could contribute to the discrepancy.

TABLE 2. Components of metabolizable energy (ME) supply in dairy cows at 4 wk postpartum.[1]

Variable	Mean
DMI, kg/d	14.5
4% FCM, kg/d	31.9
ME intake, Mcal/d	39.6
ME required,[2] Mcal/d	56.8
Portal-drained visceral net flux of energy, Mcal/d	
Acetate	7.7
Propionate	6.3
Butyrate	1.2
Other VFA	1.6
Lactate	1.5
β-Hydroxybutyrate	2.5
α-Amino N	4.0
Oxygen	6.0
Total measured flux	30.8
% of ME intake	77.8
Estimated ME from dietary fatty acids,[3] Mcal/d	3.4
Total accountable dietary ME,[4] Mcal/d	34.2
% of ME intake	86.4
Estimated energy from mobilized NEFA,[5] Mcal/d	10.0
Total accountable ME,[6] Mcal/d	44.2
% of ME required	77.8

[1]Adapted from Reynolds et al. (87, 88).

[2]Calculated from BW and milk production according to NRC (75).

[3]Assumed diet contained 3% total fatty acids that were 70% digestible.

[4]Total measured energy flux from portal-drained viscera plus estimated energy from dietary fatty acids.

[5]Estimated from plasma NEFA according to equation from Pullen et al. (83).

[6]Total accountable dietary ME plus estimated energy from mobilized NEFA.

TABLE 3. Comparison of partitioning of metabolizable energy (ME) estimated from experimental data with proposed optimal values.

Type of nutrients	Proposed optimum[1]	Estimated experimental[2]
	(% of total ME supply)	
Aminogenic	16	13.2
Glucogenic	29[3]	22.2[4]
Ketogenic	39	34.4[5]
Long-chain fatty acids		
Exogenous	16	7.6[6]
Endogenous (NEFA)	—	22.6[7]
Total	16	30.2

[1]From Kronfeld (62).

[2]From data of Reynolds et al. (87, 88) as adapted in Table 2.

[3]Glucose plus propionate.

[4]Includes portal-drained viscera (PDV) fluxes of energy from propionate, lactate, isobutyrate, and 60% of 2-methylbutyrate and valerate, plus 18% of PDV oxygen utilization.

[5]Includes PDV fluxes of energy from acetate, butyrate, β-hydroxybutyrate, 3-methylbutyrate, and 40% of 2-methylbutyrate and valerate, plus 52% of PDV oxygen utilization.

[6]Estimated assuming that diet contained 3% total fatty acids that were 70% digestible.

[7]Estimated from plasma NEFA concentration using equation of Pullen et al. (83).

The ME requirement for cows in this study, based on milk production and BW (87) as calculated from NRC values (75), was 56.8 Mcal. Much of the energy deficit between ME required and dietary ME accounted for as absorbed nutrients must have been contributed by mobilized NEFA. Based on data of Pullen et al. (83) relating NEFA concentrations to NEFA irreversible loss, mobilization of NEFA would be estimated to supply another 10.0 Mcal of ME daily. Combined with the estimate of absorbed energy supply (34.2 Mcal) the total estimated ME available to the cow would be 44.2 Mcal, or 77.8% of calculated ME requirements. The magnitude of difference suggests that either the values for absorbed nutrients were underestimated by Reynolds et al. (87, 88), or that the calculation of mobilized NEFA from NEFA concentrations (83) underestimated NEFA actually mobilized.

Kronfeld (62) proposed that for optimal health and productive efficiency the mixture of fuels constituting ME should consist of about 16% aminogenic compounds, 5% absorbed glucose, 24% propionate, 39% acetate plus butyrate and their derivatives, and 16% exogenous long-chain FA. Some experimental evidence in support of these suggestions has been obtained in studies in which increasing amounts of ruminally protected lipid were added to diets of dairy cows during early lactation (14, 17). A comparison of estimates derived from data of Reynolds et al. (87, 88) with the suggested optimal nutrient profile (62) is presented in Table 3. These values were calculated assuming that isobutyrate was glucogenic, that 3-methylbutyrate was ketogenic, and that both 2-methylbutyrate and valerate were 40% ketogenic and 60% glucogenic. Mobilized NEFA were considered to be equivalent to exogenous long-chain FA, although it might be argued that endogenous NEFA would better be considered in the same metabolic pool as acetate and butyrate.

Several insights can be gained from this exercise that are relevant to the current discussion. First, the provision of aminogenic nutrients as a percentage of ME in the study by Reynolds et al. (87, 88) was lower than the optimum suggested by Kronfeld (62). Total dietary N in the Reynolds et al. (87) study was lower than NRC (75) recommendations. As discussed by Reynolds et al. (87), the measured flux of amino-N was insufficient to account for milk N and urinary N excretion, and body N balance was negative in these cows. In addition to a deficient dietary supply, possible explanations include provision of AA to the mammary gland as peptides or a larger supply of AA from body protein than generally appreciated. Thus, if fat were added to the diet fed in this study, its utilization could be limited by an insufficient supply of AA.

Second, even though cows in the Reynolds et al. (87, 88) study were fed a diet that would be considered to be highly glucogenic (63), the supply of glucogenic compounds was substantially less then the estimated optimum proportion of calories, and the supply of acetate and butyrate and derivatives was closer to optimal. Coupled with the extensive supply of long-chain FA from the diet and from mobilized NEFA, lipogenic compounds actually available to the cows should have been more than sufficient. In contrast, despite the highly glucogenic diet, the availability of glucogenic compounds was calculated to be deficient. These data cast doubt on the validity of the theory (63) that highly glucogenic diets may actually predispose cows to ketosis by stimulating milk synthesis and resulting in a shortage of lipogenic precursors.

Finally, the supply of long-chain FA in the Reynolds et al. (87, 88) study, from the combination of dietary FA and mobilized NEFA, was far in excess of the optimum percentage of ME estimated by Kronfeld (62). Thus, even without supplementation of fat to the diet, more long-chain FA were available for metabolism in these cows (87, 88) than could be utilized efficiently as predicted by Kronfeld (62, 63). If supplemental fat were added to the diet in this study (87, 88) and it partially suppressed NEFA mobilization, total long-chain FA available for metabolism still would exceed the proposed optimal amounts. The situation would be accentuated if actual NEFA mobilization was underestimated as discussed. Consequently, regardless of whether mobilized NEFA were considered to be in the

same metabolic pool as exogenous long-chain FA or in that of acetate plus butyrate, additional dietary long-chain FA during this time period would not contribute to an improved mix of fuels constituting ME as postulated by Kronfeld (63).

What are the implications of these calculations for transition cows? If we assume that the data of Reynolds et al. (87, 88) are reasonably representative of nutrient supply in transition cows fed a diet that might be predicted to benefit from supplemental fat (i.e., low fat content, highly glucogenic), and that the estimates of Kronfeld (62) for the optimal mix of fuels for dairy cows also are reasonably accurate, supplemental fat during this time of extensive NEFA mobilization would further imbalance the mixture of fuels rather than benefit the cows. The expansion of the pool of long-chain FA in the body thus could contribute in some way to a "nutrient imbalance satiety factor" (80) that would tend to suppress intake of fat-supplemented diets during the early postpartum period. Such a scenario may explain the general lack of response to supplemental fat during the postpartum transition period (45).

Given the nature of the data available and the numerous assumptions made in making the estimates of fuel supply in periparturient cows, these calculations should be viewed as an exercise from which to develop testable hypotheses. From a practical standpoint, however, these estimates would argue for closer attention to increasing supply of absorbable AA and glucogenic precursors and minimizing the use of supplemental fat during the early postpartum period. Although general recommendations have been to increase RUP content of diets containing fat and in diets for early lactation cows, benefits have been difficult to demonstrate experimentally (82).

CHALLENGES FOR THE FUTURE

Our understanding of the biology of transition cows is in its infancy relative to the knowledge base of cows at peak lactation or beyond. Research attention to this critical area has virtually exploded in the last few years and substantial progress is likely during the next decade. Some areas in which increased understanding is critical include 1) the control of DMI during the periparturient period, 2) quantification of nutrient supply during this period when DMI and gut capacity are changing rapidly, 3) interactions among nutrition, metabolism, and the immune system, 4) metabolic regulation in, and interactions among, liver, adipose tissue, muscle, and the digestive tract in support of the initiation of lactation, and 5) effects of body condition on transition success and metabolic responses to different transition management strategies.

A major challenge for the future is to better understand how nutrition and feeding management during the far-off dry period and the close-up or transition period impact the ability of cows to make smooth transitions to lactation. Our recent findings that prepartum intake has a major effect on postpartum DMI and periparturient lipid metabolism have raised many new questions about control of DMI, incidence of health disorders, and practical transition management. How do our findings that restricted nutrient intake during the dry period result in increased DMI after parturition (23) fit with recent results of others (74) in which increasing energy intake from diets high in nonfiber carbohydrates before parturition improved transition success? Perhaps the duration of the two approaches is critical; restricted feeding during the early dry period and increased energy intakes during the late prepartal period may be complementary, not exclusive. Researchers must answer this and many other questions to push back the frontier of transition cow biology.

ACKNOWLEDGMENTS

My sincere thanks and public recognition go to all the graduate students and staff members that have contributed to the research discussed in this article. I also thank my faculty colleagues in the Department of Animal Sciences, University of Illinois, for their strong support and collaboration during my first 10 years as a faculty member.

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