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Regulation of Organic Nutrient Metabolism During Transition from Late Pregnancy to Early Lactation[1,2]

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ABSTRACT: Conceptus energy and nitrogen demands in late pregnancy are mostly met by placental uptake of maternal glucose and amino acids. The resulting 30 to 50% increase in maternal requirements for these nutrients is met partly by increased voluntary intake and partly by an array of maternal metabolic adaptations. The latter include increased hepatic gluconeogenesis from endogenous substrates, decreased peripheral tissue glucose utilization, increased fatty acid mobilization from adipose tissue, and, possibly, increased amino acid mobilization from muscle. Within 4 d of parturition, mammary demands for glucose, amino acids, and fatty acids are severalfold those of the pregnant uterus before term. Even unusual postparturient increases in voluntary intake cannot satisfy this increased nutrient demand. Therefore, rates of hepatic gluconeogenesis and adipose fat mobilization are greatly accelerated. Concomitant changes in amino acid metabolism include increased hepatic protein synthesis and, possibly, decreased amino acid catabolism, and increased peripheral mobilization of amino acids. Insulin resistance in adipose tissue and muscle, developed during late pregnancy, continues postpartum; adipose lipolytic responsiveness and sensitivity to adrenergic agents are increased postpartum beyond their levels during late pregnancy. Before parturition, these homeorhetic adjustments may be coordinated with lactogenesis by increased secretion of estradiol and prolactin. Their amplification and reinforcement at and soon after parturition may be regulated mostly by somatotropin.

Key Words: Dairy Cows, Pregnancy, Lactation, Metabolic Adaptations, Homeorhesis

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Introduction

The period of transition between late pregnancy and early lactation presents an enormous metabolic challenge to the high-yielding dairy cow. Failure to adequately meet this challenge can result in a range of early postpartum health problems, some potentially fatal, and compromised lactation performance, as discussed elsewhere in this symposium (Grummer, 1995). Nutritional and other strategies to facilitate the periparturient transition should be based on a thorough understanding of the quality and quantity of nutrients required to support conceptus growth during late pregnancy and milk synthesis during early lactation. The homeorhetic regulation of metabolic changes in nonuterine and nonmammary tissues, such as liver and adipose tissue, is also a vitally important consideration.

Therefore, a first objective of this review is to describe and quantitatively compare the specific nutrient requirements of the gravid uterus in late pregnancy and the lactating mammary gland within days of parturition. A second objective is to develop a conceptual framework for understanding how the complex array of metabolic adaptations in other key tissues is regulated and coordinated before and after parturition.

Metabolism in Late Pregnancy

Conceptus Metabolism and Nutrient Requirements

During the last 25 yr, great progress has been made in quantitative, in vivo studies of uterine, fetal, and placental metabolism in ruminants. The overwhelming majority of these have been done on sheep (see reviews Battaglia and Meschia, 1988; Bell, 1993), with the series of studies on pregnant beef cows by Ferrell and his colleagues representing the only sustained investigation of bovine conceptus metabolism (Ferrell et al., 1983; Reynolds et al., 1986; Ferrell, 1991). These papers, together with the only similar published study on a dairy breed, the Jersey

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(Comline and Silver, 1976), provide the quantitative basis of this section, with metabolic data scaled to rates of conceptus growth observed in Holsteins (Bell et al., 1992). Where appropriate, more detailed metabolic information has been drawn from studies on sheep.

The ultimate metabolic impact of the conceptus on its dam is best represented in terms of the nutrient requirements of the whole gravid uterus (i.e., uterine tissues, placenta, fetal membranes and fetus[es]). These are described later in this section. First, however, the specific requirements and metabolic characteristics of the fetus and its supporting uteroplacental tissues are separately discussed. Methodological approaches for the functional separation of these components in vivo are discussed elsewhere (Battaglia and Meschia, 1988; Bell, 1993).

Fetal Metabolism. During late pregnancy, fetal metabolic rate, represented as weight-specific oxygen consumption, is approximately twice that of the dam (Reynolds et al., 1986). Most of the carbon and nitrogen required for fetal growth and metabolism is supplied by glucose (directly and via its fetal-placental intermediate, lactate) and amino acids. This is clearly evident in Table 1, in which metabolic balance sheets for specific nutrient contributions to energy and nitrogen requirements in the late-gestation bovine fetus are presented. The debit and credit sides of the metabolic ledger balance surprisingly well, despite considerable uncertainty about some of the estimates.

Direct measurement of fetal oxidation of glucose and lactate indicates that in well-fed ewes these substrates account for no more than 50 to 60% of fetal respiration (Hay et al., 1983). Placental transport of short- and long-chain fatty acids and ketones is limited in ruminants (Bell, 1993). Fetal uptake of maternal acetate was estimated to contribute, at most, 10 to 15% of fetal respiratory fuel in late-pregnant cows (Comline and Silver, 1976). The remaining 30 to 40% of substrate for oxidation seems to be amino acids, which, based on measurements of fetal urea production, are extensively catabolized by the well-nourished fetus (Faichney and White, 1987). This would seem to be an unusual metabolic situation in a rapidly growing organism. However, it is consistent with observations that fetal protein deposition accounts for, at most, 50% of the fetal net uptake of amino acids in sheep (Lemons et al., 1976; Meier et al., 1981) and cattle (Reynolds et al., 1986; Ferrell, 1991). In fact, the data summarized in Table 1 suggest that only 32% of amino acid nitrogen taken up by the late-gestation bovine fetus is deposited in tissue protein. This means that the fetal requirement for metabolizable amino acids is approximately three times the net requirement for fetal growth. For example, we recently reported an average rate of crude protein deposition of 74 g/d in Holstein fetuses between d 190 and 270 of gestation, with a projected mean birth weight of 45 kg (Bell et al., 1992). From this, the metabolizable amino acid requirement for fetal growth was estimated to be about 220 g/d.

In contrast, the nutrient requirement for fat deposition in fetal ruminants is relatively insignificant. In our Holstein cow study, the average rate of fetal fat deposition during late pregnancy was a mere 12 g/d (Bell et al., 1992), accounting for less than 5% of the estimated fetal energy requirement (Table 1). This is consistent with the low body fat content (< 30 g/kg) of newborn calves (Ellenberger et al., 1950). In sheep, which are similarly lean at birth, the modest rate of fetal fat deposition has been attributed to placental impermeability to preformed long-chain fatty acids in the maternal circulation (Elphick et al., 1979) and a greatly reduced capacity for de novo fatty acid synthesis in fetal adipose tissue during late pregnancy (Vernon et al., 1981b).

Placental and Uterine Metabolism. The uteroplacental tissues (placentomes, endometrium, myometrium) account for less than 20% of the weight of the gravid uterus during late pregnancy. However, they consume 35 to 50% of oxygen and at least 65% of glucose taken up by the uterus in ewes (Meschia et al., 1980) and cows (Reynolds et al., 1986). As previously discussed (Bell, 1993), most of this relatively intense metabolic activity must be confined to the placenta because most of the maternal and fetal blood perfusing the uteroplacental tissue mass is distributed to the placentomes.

Although much of the glucose taken up by the uteroplacenta is undoubtedly oxidized to completion, a considerable fraction (30 to 40%) is converted to lactate, which is released into maternal and fetal circulations (Meschia et al., 1980; Reynolds et al., 1986). Radiotracer studies have shown that the fetal

Table 1. Fetal sources and requirements of energy and nitrogen in late-pregnant cows[2]

Item	Energy, kcal/d	Nitrogen, g/d
Sources		
Glucose and lactate[bcd]	775	—
Amino acids[d]	1,306	38
Acetate[b]	255	—
Total	2,336	38
Requirements		
Tissue deposition[e]	605	12
Heat[bd]	1,605	—
Urea[d]	125	23
Total	2,335	35

[a]Data from different breeds are scaled to a fetal weight of 35 kg at 250 d of pregnancy to represent the Holstein breed (Bell et al., 1992).
[b]Comline and Silver (1976).
[c]Reynolds et al. (1986).
[d]Ferrell (1991).
[e]Bell et al. (1992).

portion is derived from metabolism of fetal glucose and therefore represents recycling of fetal glucose carbon within the fetal-placental unit. In contrast, lactate released into the maternal circulation is derived from caruncular and uterine tissue metabolism of maternal glucose (Bassett, 1986). An additional, smaller fraction of glucose taken up by the fetal placenta is metabolized to fructose and released back into the umbilical circulation. The high blood concentrations of this hexose in fetal ruminants is more a consequence of slow fetal clearance and metabolism than of rapid placental production (Meznarich et al., 1987).

Bovine placental growth continues into late pregnancy, at least until approximately 230 d (Ferrell et al., 1976; Bell et al., unpublished data). However, the rate of growth is modest, accounting for a net accretion of no more than about 7 g/d of CP. Greater rates of uteroplacental consumption of amino acids have been reported (Reynolds et al., 1986; Ferrell, 1991), implying considerable placental catabolism. The nature of this process remains uncertain in cattle, although some enzymatic capacity for placental ureagenesis has been reported (Ferrell, 1988). The sheep placenta, which does not grow at all during late pregnancy, also has a net consumption of some amino acids, specifically the branched-chain acids plus glutamine and citrulline (Liechty et al., 1991). It actively deaminates leucine and probably other amino acids (Battaglia, 1992), yielding ammonia that is both used for placental synthesis of glutamine from glutamate (Holzman et al., 1979) and released in free form into maternal and fetal circulations (Holzman et al., 1977).

To summarize, the nonfetal components of the gravid uterus, especially the placenta, account for large fractions of uterine oxygen and glucose consumption in cattle and sheep. In cows, but not in ewes, the uteroplacental net consumption of amino acids is puzzlingly high. The gravid uterus also takes up modest amounts of acetate and 3-hydroxybutyrate, metabolism of which is mostly confined to the (presumably) maternal uteroplacental tissues (Bell, 1993).

Nutrient Partitioning Between Conceptus and Dam. Absolute rates of uterine uptake of glucose, amino acids, and acetate, and their predicted impact on maternal nutrient supply, are summarized in Table 2. Rates of maternal whole-body substrate supply were predicted for a hypothetical mature Holstein dry cow weighing 650 kg at 250 d of pregnancy. Values for DMI (11.3 kg/d), ME (25.5 Mcal/d), and metabolizable protein (998 g/d) were predicted from the known chemical composition of a commercial dry cow ration using the Cornell Net Carbohydrate Protein system (Sniffen et al., 1992). Glucose and acetate supply rates were then derived from equations relating glucose (Wieghart et al., 1986) and acetate (M. Wieghart and J. M. Elliot, unpublished data) to energy intake in Holstein cows.

Table 2. Uterine uptake in relation to maternal supply of organic nutrients in late-pregnant cows[a]

Nutrient	Maternal supply, g/d[b]	Uterine uptake[c] g/d	Uterine uptake[c] % of Maternal supply
Glucose	1,476[d]	666	46
Amino acids	998[e]	718	72
Acetate	2,196[f]	270	12

[a]Gravid uterine weight assumed to be 64 kg at 250 d of pregnancy (Bell et al., 1992).
[b]Predicted values, assuming intakes of metabolizable energy and metabolizable protein to be 25.5 Mcal/d and 998 g/d, respectively.
[c]Values calculated on basis of uterine weight from data of Comline and Silver (1976), Reynolds et al. (1986), and Ferrell (1991).
[d]Total splanchnic glucose entry rate (Wieghart et al., 1986).
[e]Metabolizable protein predicted using Cornell Net Carbohydrate Protein System (Sniffen et al., 1992).
[f]Posthepatic appearance of acetate (M. Wieghart and J. M. Elliot, unpublished data; same experimental conditions as Wieghart et al., 1986).

The estimation that uterine uptake accounts for approximately half of maternal glucose supply (Table 2) agrees well with our direct observations in monotocous ewes that were carefully fed to predicted energy requirements in late pregnancy (Leury et al., 1990). However, the estimated values for uterine uptake of amino acids and acetate may have overstated the uterine contribution to whole-body utilization of these nutrients. Uterine uptake of amino acids was calculated from data on uterine exchange for α-amino nitrogen (Reynolds et al., 1986; Ferrell, 1991). In an earlier paper by this group (Ferrell and Ford, 1980), the uterine net uptake of aggregated individual amino acids was considerably less than that of α-amino nitrogen. In well-fed, late-pregnant ewes, uterine uptake of acetate was estimated to account for only 3 to 4% of maternal acetate utilization (Bell, 1993).

Effects of Energy and Protein Nutrition. As discussed above, the energy and nitrogen requirements of the ruminant conceptus are met almost exclusively by placental uptake of glucose and amino acids from the maternal circulation. Because placental glucose transport occurs by facilitated diffusion (Stacey et al., 1978), it is dependent on the maternal-fetal plasma glucose concentration gradient and is thus responsive to changes in maternal glycemia. Energy-deprived ewes, and presumably cows, are especially susceptible to hypoglycemia during late pregnancy (Bergman, 1973), which leads to reductions in uterine and fetal uptake of glucose (Hay et al., 1984; Leury et al., 1990).

In contrast, maternal undernutrition (or at least, fasting for 5 d) has little effect on fetal uptake of amino acids in late-pregnant ewes (Lemons and Schreiner, 1983), presumably because the active placental transport of most amino acids is largely independent of changes in maternal blood concentration (see Bell, 1993). However, the metabolic fate of

this relatively unchanged fetal supply of amino acids is markedly altered. Most, if not all, of the deficit in glucose available for oxidation is made up by increased catabolism of amino acids, at the expense of protein synthesis and deposition in fetal tissues. The outcome is reduced fetal growth associated with increased synthesis and placental excretion of urea (Lemons and Schreiner, 1983).

Specific metabolic responses of the conceptus to maternal protein deprivation have not been studied in sheep or cattle. However, we recently observed that fetal growth between 110 and 140 d was decreased by approximately 20% in twin-pregnant ewes fed a diet low in protein (8% CP) but adequate in energy, compared with ewes fed a protein-adequate diet (12% CP) over the same period in late pregnancy (McNeill et al., 1994). This implies that placental capacity to sustain amino acid transport in the face of a dwindling maternal supply is not unlimited. Thus, whether glucose or amino acids are primary limiting nutrients for fetal growth during maternal energy or protein deprivation, respectively, the availability of amino acids for fetal tissue protein synthesis seems to be of central importance.

Maternal Metabolic Adaptations

Maternal strategies for accommodating the substantial glucose and amino acid requirements of the conceptus include changes in not only carbohydrate and protein metabolism, but also lipid metabolism. The conceptus, or at least its fetal portion, cannot take direct advantage of lipid substrates mobilized by its dam. However, increased maternal metabolism of these substrates serves to spare maternal utilization of glucose and, perhaps, amino acids for use by the conceptus.

Patterns of Nutrient Metabolism. Any adaptive changes in maternal nutrient metabolism during late pregnancy must be considered in relation to maternal nutrition. For example, rates of whole-body glucose production (mainly hepatic gluconeogenesis) in late-pregnant ewes with ad libitum access to feed generally exceed those of nonpregnant sheep with ad libitum access to feed (Steel and Leng, 1973). Some of this greater glucogenesis is due to increased voluntary feed intake, especially of good-quality rations. However, it also occurs in ewes on restricted rations, in which glucose production increases with both stage of pregnancy and fetal number (Steel and Leng, 1973; Wilson et al., 1983). The latter is presumably possible via increased hepatic uptake of endogenous glucogenic substrates such as amino acids, glycerol, and, perhaps, lactate. As discussed by Bell (1993), evidence for a pregnancy-induced reduction in glucose uptake by peripheral tissues is conflicting, but this disagreement may also be reconciled by variations in nutrition. In at least one study in which feed intake was controlled and adequately described, glucose utilization by hind-limb muscle was reduced in late-pregnant ewes fed close to predicted energy requirements; net release of lactate from muscle was also increased (Hough et al., 1985). This, in addition to the lactate released from the gravid uterus in ewes (Meschia et al., 1980) and cows (Comline and Silver, 1976; Reynolds et al., 1986), contributes to the greater rate of lactate production and Cori cycling in pregnant ruminants (Baird et al., 1983).

There is little published information on acetate metabolism in nonuterine tissues of pregnant ruminants. An analysis of several preliminary reports and unpublished sources suggests that acetate supply is, predictably, determined by DE intake, and that acetate uptake and oxidation by skeletal muscle may decline in late pregnancy, presumably because feed intake does not match the increased energy need at this time (Bell, 1993).

Circulating levels of nonesterified fatty acids (NEFA) and ketones tend to be elevated during late pregnancy, even in animals carefully fed to predicted energy requirement for conceptus growth and maintenance of nonuterine tissues (Petterson et al., 1994). This trend becomes more evident close to term and is sharply exaggerated if energy intake is voluntarily or involuntarily restricted (Reid and Hinks, 1962; Radloff et al., 1966; Petterson et al., 1994). Uptake and oxidation of NEFA by the liver and extrahepatic tissues, including skeletal muscle, are directly related to plasma concentration in pregnant ewes (Katz and Bergman, 1969; Pethick et al., 1983). Hepatic ketogenesis via incomplete oxidation of NEFA almost certainly accounts for any moderate increase in 3-hydroxybutyrate concentration (Bell, 1981) that, within the physiological range, has a direct influence on uptake and oxidation of 3-hydroxybutyrate by peripheral tissues, including the gravid uterus (Pethick and Lindsay, 1982).

Effects of pregnancy on the quantitative metabolism of amino acids have not been systematically studied in ruminants. However, in agreement with data from laboratory animals (Ling et al., 1987), we have preliminary evidence of increased hepatic protein synthesis in preparturient dairy cows despite unchanged or declining protein intake (N. J. Gannon, P. J. Reeds, J. E. Nocek, and A. W. Bell, unpublished data; Figure 1). This is consistent with the moderate liver hypertrophy observed in late-pregnant ewes (Campbell and Fell, 1970). Despite an increase in protein intake, late-pregnant ewes were, in one study at least, found to have reduced blood urea concentrations compared with nonpregnant controls (Herriman et al., 1976), implying a reduction in hepatic amino acid catabolism.

The possibility of pregnancy-specific adaptations in amino acid metabolism of posthepatic tissues, particularly skeletal muscle, should also be examined. Proteolytic activity in and amino acid release from

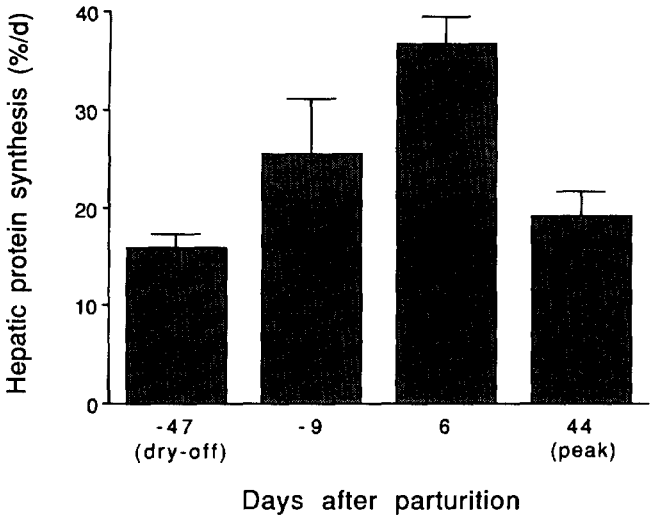

Figure 1. Fractional protein synthetic rate in liver of Holstein cows at different stages of the reproduction-lactation cycle. Histograms are means and bars are SEM for the same four cows measured at each stage (N. J. Gannon, P. J. Reeds, J. E. Nocek, and A. W. Bell, unpublished data obtained using the stable isotopic infusion method of Gannon et al., 1994, and repeated liver biopsy).

maternal muscle are increased in late-pregnant rats (Amin and Shafrir, 1983; Ling et al., 1987). A substantial capacity for mobilization of amino acids from maternal tissues in ruminants can be inferred from our observation of decreased tissue protein stores and semitendinosus muscle weight in ewes fed a low-protein diet (8% CP) during late pregnancy (McNeill et al., 1994).

To summarize, metabolic patterns in maternal tissues of well-fed, late-pregnant ruminants are characterized by increased hepatic gluconeogenesis but reduced glucose utilization in peripheral tissues, unchanged or decreased peripheral utilization of acetate, and moderately increased mobilization of NEFA from adipose tissue, associated with similar increases in peripheral utilization of NEFA and their hepatic metabolite, 3-hydroxybutyrate. Specific changes in amino acid metabolism have not been characterized but may include increased protein synthesis and reduced amino acid catabolism in the liver and a greater predisposition to muscle proteolysis. All of these observed or putative metabolic adaptations are consistent with promotion of availability of glucose and amino acids for conceptus metabolism and increasing reliance of maternal tissues on NEFA and ketones for oxidative metabolism. Their successful operation seems to account for the ability of moderately, but not seriously, undernourished dams to maintain a uterine glucose supply that is adequate to support normal conceptus growth in late pregnancy (for data and more detailed discussion, see Bell, 1993). This, of course, can only occur at the expense of maternal lipid and protein reserves.

Metabolism During Lactogenesis and Early Lactation

Lactogenesis is conveniently considered to be a two-stage process. The first stage involves mammary differentiation and limited synthesis and secretion of pre-colostrum for some weeks before parturition; the second involves the onset of copious milk secretion just before parturition and extends for several days postpartum (Fleet et al., 1975; Tucker, 1985). Specific nutrient requirements for mammary functions and their impact on whole-body metabolism during the first stage are small and will not be separately considered here. Rather, the focus of this section will be on metabolic events during the second stage of lactogenesis. However, an important thesis of this review is that several of the metabolic adaptations initiated and gradually amplified during stage one (discussed earlier in the context of late pregnancy) are essential preludes to the major metabolic shifting of gears required during stage two.

Mammary Metabolism and Nutrient Requirements

Numerous studies have described, on the one hand, changes in mammary secretory activity (e.g., Fleet et al., 1975) and on the other, more detailed changes in enzyme activities and cellular metabolism of mammary tissues (e.g., Kuhn, 1983) before and after parturition. However, very few have dealt with ongoing changes in mammary metabolism in vivo during the periparturient period. A notable exception is the study of Davis et al. (1979), who measured mammary blood flow and oxygen and nutrient uptake in goats at frequent intervals between d 7 to 9 prepartum and d 6 postpartum. Mammary blood flow, oxygen consumption, and uptake of glucose and acetate increased markedly between 2 d and .5 to 1 d prepartum, before further major increases on d 1 postpartum (Figure 2). The relative increase in glucose uptake was much greater than that of blood flow, oxygen consumption or acetate uptake. The authors concluded that the magnitude and timing (.5 to 1 d prepartum) of this increase is an important index of the onset of copious milk secretion because glucose is required for lactose synthesis and lactose is the most important osmotic solute in milk.

It is especially notable that mammary glucose uptake on the day after parturition was nine times that on d 7 to 9 prepartum and five times that on d 2 prepartum (Figure 2). Neither feed intake nor whole-body glucose production rate was reported. However, the impact of this sudden increase in glucose demand is highlighted by the reasonable assumptions that

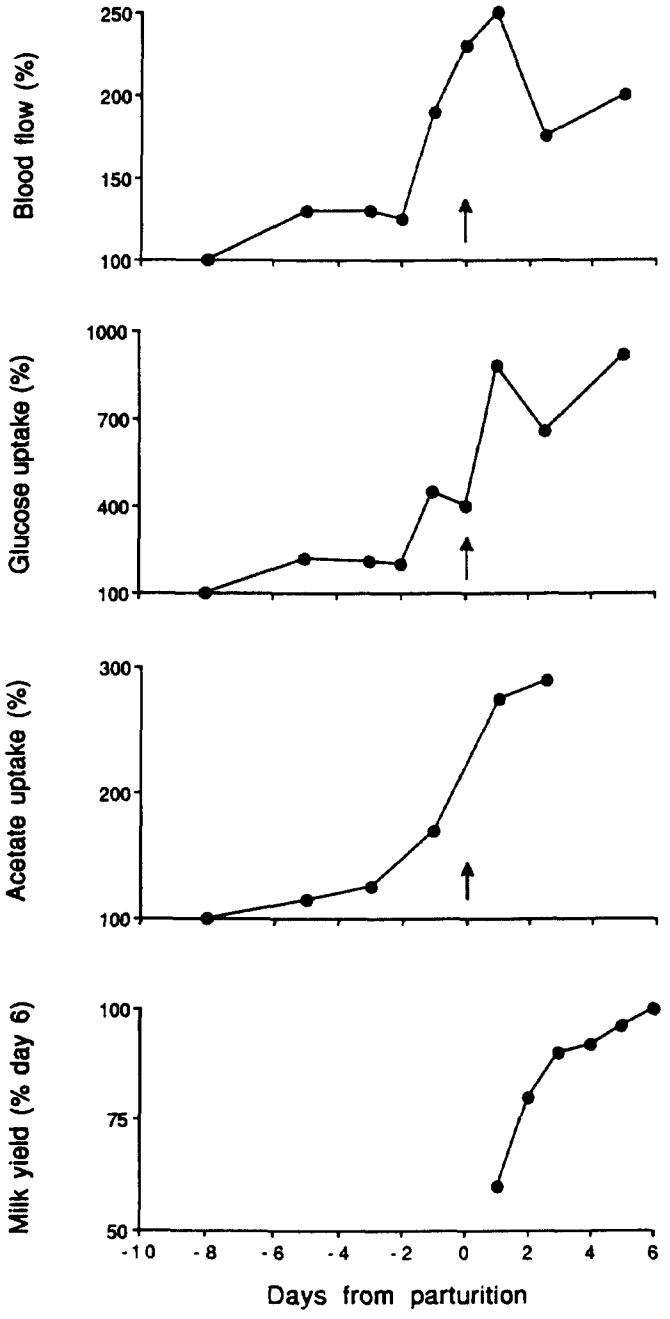

Figure 2. Mammary blood and nutrient uptake, expressed as a percentage of values on d 8 prepartum, and milk yield, expressed as a percentage of the value on d 6 postpartum, in periparturient Saanen goats. Adapted from Davis et al. (1979).

voluntary feed intake did not increase appreciably before d 1 postpartum, and that the mammary uptake of glucose (approximately 110 g/d) at this time is as great as whole-body glucose production of a maintenance-fed, nonpregnant, nonlactating goat (Baile et al., 1969).

To further emphasize the need for substantial metabolic adjustments during lactogenesis, it is

Table 3. Lactation performance and predicted mammary uptake of major organic nutrients in Holstein cows at 4 days postpartum[a]

Milk yield, kg/d[b]			29.6 ± .8
Milk fat, g/kg[b]			46.7 ± 1.9
Milk protein, g/kg[b]			42.3 ± 1.6
	g/d	Mcal/d	g of N/d
Mammary uptake			
Glucose[c]	1,775	6.6	—
Amino acids[d]	1,374	8.0	220
Fatty acids[e]	1,224	11.3	—

[a]Performance data provided by W. R. Butler and S. Beam, Cornell University, Ithaca, NY.
[b]Means ± SE for 34 multiparous cows.
[c]Assumed milk lactose concentration of 48 g/kg, and that total mammary glucose requirement is 1.25 times that required for lactose synthesis.
[d]Assumed mammary uptake of amino acids is 1.1 times milk protein secretion.
[e]Assumed mammary uptake of fatty acids is .9 times milk fat secretion.

instructive to compare early postparturient mammary requirements for glucose, amino acids, and fatty acids with preparturient conceptus requirements of these substrates. Sequential measurements of uterine glucose uptake in late pregnancy and mammary glucose uptake in early lactation have been made on the same ewes (Oddy et al., 1985). However, milk yields of these animals were too low for realistic extrapolation of results to the high-yielding dairy cow. Therefore, values for mammary organic nutrient and energy requirements have been estimated from performance data of 34 Holstein cows from the Cornell University herd at 4 d postpartum (Table 3; primary data provided by courtesy of W. R. Butler and S. Beam). In Figure 3, these estimates are compared to those summarized in Table 2 for uterine uptake of the same nutrients for a Holstein cow at 250 d of pregnancy. The latter values are assumed to be representative of uterine nutrient utilization closer to term (approximately 280 d) because bovine fetal and conceptus growth rates, and thus nutrient requirements, are at best constant (Bell et al., 1992), and may even decline after 250 d (Prior and Laster, 1979). It is apparent that within a few days of calving, mammary requirements for glucose, amino acids, and fatty acids are, respectively, approximately 2.7, 2.0, and 4.5 times those of the gravid uterus during late pregnancy, and the estimated mammary requirement for energy is three times that of the uterus.

As discussed in a previous section, it is possible that in experiments on cows, uterine (more specifically, uteroplacental) utilization of amino acids has been overestimated. If so, the margin between mammary and uterine requirements for these vital nutrients, and its consequent periparturient impact on the dam, will be even greater. The estimated values for fatty acid uptake also require qualification. It is assumed that acetate is the only short- or long-chain fatty acid

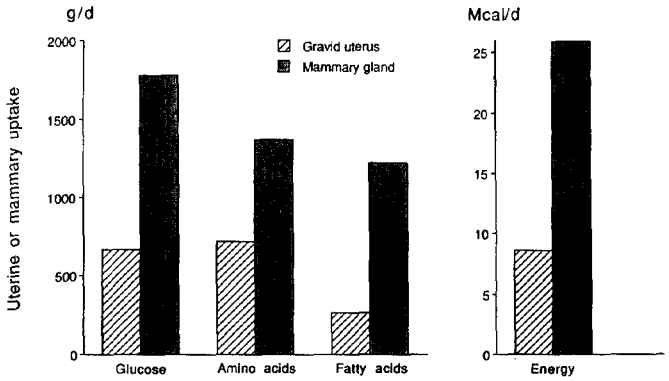

Figure 3. Comparison of estimated values for uterine uptake of specific nutrients and energy at d 250 of pregnancy, and mammary uptake of these nutrients and energy at d 4 postpartum, in Holstein cows. See text for details of calculations.

taken up in significant quantities by the pregnant uterus (for rationale, see Bell, 1993). The present predicted value for mammary uptake of fatty acids is a minimal estimate, based simply on the assumed fatty acid composition of measured values for milk fat secretion; actual uptake is almost certainly greater. During established lactation, approximately half of the fatty acids in milk triglycerides are derived via mammary de novo synthesis from acetate and 3-hydroxybutyrate; the remaining half are derived preformed from plasma lipoprotein triglycerides (Bickerstaffe et al., 1974). However, during early lactation, when cows are in negative energy balance and circulating levels of NEFA are relatively high, mammary uptake of NEFA may account for a significant fraction of milk fat synthesis (Pullen et al., 1989; Miller et al., 1991b). This may be most important during the very early postpartum period when plasma NEFA concentrations are especially high (Grummer, 1993). In fact, it is predicted that in the cows described above (Table 3), NEFA could have accounted for as much as 40% of milk fatty acids on d 4 postpartum. This prediction is based on their mean plasma NEFA concentration of 770 μmol/L (W. R. Butler and S. Beam, unpublished data) and the linear relation between mammary extraction and arterial plasma concentration of NEFA in Holstein cows over a wide range of metabolic states (Miller et al., 1991a). It is also consistent with the high milk fat content (47 g/L) of these cows, and the positive correlation between plasma NEFA and milk fat content (Pullen et al., 1989). An additional endogenous source of fatty acids for mammary metabolism are the very-low-density lipoproteins (**VLDL**), derived from NEFA taken up by the liver. However, their contribution to milk fat synthesis in early lactation is small (Pullen et al., 1989) and can, in any case, be discounted against NEFA metabolism.

Table 4. Dry matter intake (DMI), diet composition, and predicted nutrient supply in Holstein cows during late pregnancy and early lactation

Item	Pregnant[a]	Lactating[b]
DMI, kg/d	11.3	14.6
Diet composition		
ME, Mcal/kg DM	2.25	2.60
CP, g/kg DM	125	175
NDF, g/kg DM	430	355
Predicted postabsorptive supply, g/d		
Glucose[cd]	1,476	2,089
Acetate[ce]	2,196	3,249
Propionate[cf]	614	878
Amino acids[g]	998	1,650

[a]Cows described in Table 2.
[b]Cows described in Table 3.
[c]Predicted from values for energy intake.
[d]Total splanchnic glucose entry rate (Wieghart et al., 1986).
[e]Posthepatic appearance of acetate (M. Wieghart and J. M. Elliot, unpublished data; same experimental conditions as Wieghart et al., 1986).
[f]Portal appearance of propionate (M. Wieghart and J. M. Elliot, unpublished data; same experimental conditions as Wieghart et al., 1986).
[g]Metabolizable protein predicted using Cornell Net Carbohydrate Protein System (Sniffen et al., 1992).

Mammary Nutrient Demands vs Whole-Body Supply

On d 4 of lactation, the cows described in Table 3 ate 14.6 kg of DM containing approximately 35 Mcal of ME and 2.5 kg of CP. Rates of posthepatic glucose supply and portal appearance of acetate and propionate were predicted from equations relating these variables to energy intake in lactating Holstein cows (Wieghart et al., 1986; M. Wieghart and J. M. Elliot, unpublished data); metabolizable protein (= absorbed amino acids) was predicted by the Cornell Net Carbohydrate Protein system (Sniffen et al., 1992). In Table 4, these values are compared with those predicted for the hypothetical late-pregnant, nonlactating cow summarized in Table 2. The immensity of the metabolic challenge facing the periparturient cow becomes apparent when predicted increases in dietary supply of glucogenic and lipogenic precursors, including amino acids, are compared with the increment in mammary over uterine demands for glucose, amino acids, and fatty acids.

The predicted increase in glucose supply (Table 4) would account for little more than half of the estimated mammary over uterine increment in glucose demand (Tables 2 and 3). The estimated increase in postabsorptive amino acid supply would almost exactly satisfy the increased mammary vs uterine demand for amino acids. However, the predicted supply of metabolizable amino acids of 1,650 g/d on d 4 of lactation falls significantly short of the total requirement of approximately 2,210 g/d for maintenance and lactation specified by the Cornell Net

Carbohydrate Protein system, presumably because of a major increase in use of amino acids for hepatic gluconeogenesis, discussed in the next section. The predicted increase in acetate supply could, if entirely used for mammary lipogenesis, account for approximately 90% of the mammary increment in demand for lipogenic substrate. This assumption is, however, untenable because mammary uptake accounts for a relatively small fraction of whole-body acetate metabolism, and even within the mammary gland, a significant portion of acetate taken up is oxidized (Bickerstaffe et al., 1974). Conversely, it seems reasonable to assume that most, if not all, of the small increase in intake of dietary lipid (200 to 300 g/d) is used for mammary triglyceride synthesis.

To summarize, it is very clear that during the 1st wk of lactation there is a major shortfall in the dietary supply of nutrients required for mammary synthesis of lactose, protein, and triglyceride. To sustain the impressive early performance shown in Table 3, cows were calculated to be in very substantial negative balance for net energy (−12 Mcal/d) and metabolizable protein (−560 g/d). Specific metabolic adaptations that underlie the mobilization of tissue energy and protein reserves are discussed next.

Nonmammary Metabolic Adaptations

The metabolic challenge of the second phase of lactogenesis probably affects most organs and tissues in the body. This section will be concerned with only those most directly involved in meeting the mammary demand for endogenous substrates (i.e., adipose tissue, skeletal muscle, and liver).

Lipid Metabolism. The massive mobilization of NEFA from adipose tissue during and after parturition is the metabolic hallmark of the transition from pregnancy to lactation. Plasma NEFA concentration is a reliable index of the magnitude of this response because it is highly correlated with the rate of entry of NEFA into the bloodstream in lactating cows (Bauman et al., 1988; Pullen et al., 1989) and goats (Dunshea et al., 1989, 1990). In turn, NEFA entry rate is representative of fat mobilization from adipose tissue, and thus body fat loss (Dunshea et al., 1988), although some NEFA must be derived from nonspecific lipolysis of circulating triglycerides in mammary, and probably other, tissues (Bickerstaffe et al., 1974).

Thus, using the equation of Pullen et al. (1989), cows at d 4 of lactation (Table 3) were predicted to have a NEFA entry rate of 10.7 mol/d, based on their mean plasma NEFA concentration of 770 μmol/L. This is the equivalent of about 3.2 kg/d of triglyceride, with an energy equivalent of approximately 30 Mcal/d. Because the latter value is approximately 2.5 times the calculated negative energy balance of these cows, it is likely that a considerable fraction of mobilized NEFA is not quickly lost to oxidation and milk fat synthesis. The equation of Pullen et al. (1989) relating whole-body oxidation rate and plasma concentration of NEFA predicts the rapid oxidation of approximately 35% of NEFA entry rate. If, as predicted earlier, mammary uptake of NEFA accounts for approximately 40% of fatty acids in milk triglyceride, this would account for an additional 17% of NEFA turnover. It therefore seems that in periparturient cows about half of the NEFA released into the bloodstream are either oxidized or incorporated into milk triglycerides. Some NEFA oxidation is assumed to occur indirectly via oxidation of ketones derived by hepatic synthesis from NEFA (Pethick et al., 1983), consistent with the moderate increase in blood concentrations of 3-hydroxybutyrate in healthy postparturient cows (Vazquez-Anon et al., 1994).

Net release of NEFA from adipose tissue represents the balance between triglyceride synthesis and lipolysis. Thus, increased NEFA mobilization can be achieved in a number of ways: by suppression of the de novo synthesis or uptake, and thence esterification of fatty acids; by promotion of lipolysis; by reduction of the intracellular reesterification of fatty acids released by lipolysis; or by some combination of these metabolic changes. All three possibilities seem to be invoked in the periparturient ruminant. Adipose tissue lipogenesis and fatty acid esterification, which are already low during late pregnancy, are further suppressed during the onset of lactation in ewes (Vernon et al., 1981a; Smith and Walsh, 1984) and cows (McNamara and Hillers, 1986). Intracellular reesterification of hydrolyzed fatty acids is also minimal soon after parturition, as judged by a ratio of NEFA:glycerol release that approaches the theoretical maximum of three in bovine adipose tissue in vitro (Metz and van den Bergh, 1977), and in goats in vivo (Dunshea et al., 1990). This alone probably accounts for most of the net release of NEFA from adipose tissue during early lactation because, after the immediate postparturient period, basal lipolysis seems to be relatively unchanged in cows (McNamara and Hillers, 1986) and goats (Dunshea et al., 1990). However, as discussed in the final section of this review, the very high plasma levels of NEFA during and soon after parturition (Grummer, 1993) are presumably due in large part to greatly increased adrenergic stimulation of lipolysis at this time.

Carbohydrate and Protein Metabolism. Carbohydrate metabolism in the early postparturient cow is dominated by the massive mammary requirement for glucose, mostly for lactose synthesis. The immediacy and magnitude of this increased demand is illustrated by the doubling of glucose production rate in dairy cows on the day of calving, compared with that observed a few days prepartum (Paterson and Linzell, 1974). The challenge posed for the liver and other nonmammary tissues is apparent when estimated mammary glucose uptake at d 4 of lactation (Table 3)

is compared with the estimated supply of dietary glucose precursors (propionate and amino acids) (Table 4). Even with the unlikely assumption that all absorbed propionate (878 g/d) and amino acids (minus those required for milk protein = 276 g/d) are available for hepatic gluconeogenesis, glucose synthesized from these substrates could account for only approximately 65% of mammary glucose uptake. The supply of glycerol from adipose tissue lipolysis could, if used completely for gluconeogenesis, account for a further 15 to 20%. Lactate of dietary and endogenous origins would make a further small, but less predictable, contribution. Taking into account the extrahepatic metabolism and far from complete hepatic extraction of substrates other than propionate (Lomax and Baird, 1983), it is unlikely that glucose derived from hepatic metabolism of propionate, dietary amino acids (less mammary uptake), glycerol, and lactate could meet mammary requirements, let alone the mandatory glucose needs of other tissues. The calculated shortfall in glucogenic substrate supply will be offset somewhat by reduced glucose uptake and oxidation in nonmammary peripheral tissues (Bauman and Elliot, 1983; Hough et al., 1985). Nevertheless, an estimated deficit of at least 500 g/d remains that can apparently be made up only by mobilization of amino acids stored in skeletal muscle and other tissue proteins.

The so-called "labile protein reserve" of the lactating cow has been estimated to be approximately 25% of total body protein (Botts et al., 1979). This represents 20 to 25 kg of protein in a mature Holstein cow. However, this estimate was obtained from a long-term depletion-repletion experiment and the amount of tissue protein immediately available for mobilization during the early postparturient period is likely to be considerably less. The potential significance of mobilized tissue protein as a source of amino acids for mammary metabolism or hepatic gluconeogenesis during early lactation was discussed by Bauman and Elliot (1983). They concluded that over the period up to peak lactation, the contribution of mobilized tissue protein to total needs is small. However, it may be critical during the 1st wk or two after parturition when the cow is in substantial negative nitrogen balance. It is probably not coincidence that the estimated metabolizable protein balance of cows at d 4 postpartum (−560 g/d) is of similar magnitude to the apparent requirement of endogenous amino acids for gluconeogenesis at this time (~500 g/d).

The most likely tissue source of mobilized amino acids is skeletal muscle. Net protein loss from this tissue is indicated by a 25% reduction in muscle fiber diameter in dairy cows immediately after calving (Reid et al., 1980) and a decline in muscle protein: DNA ratio during early lactation in ewes (Smith et al., 1981). These observations are consistent with the reduction in muscle protein synthesis observed in goats that were in negative nitrogen balance during early lactation (Champredon et al., 1990; Baracos et al., 1991). By analogy with Holstein steers in negative nitrogen balance due to underfeeding, it seems likely that net release of amino acids from skeletal muscle is achieved entirely by suppression of protein synthesis rather than enhancement of protein degradation (Boisclair et al., 1993).

Peripheral mobilization of amino acids seems to be accompanied by enhanced synthetic activity and more efficient use of amino acids in the liver. In dairy cows, the periparturient increase in hepatic protein synthesis, initiated during late pregnancy, is significantly augmented soon after calving (Figure 1). This must be a necessary prelude to the substantial hypertrophic and hyperplastic growth of the liver during early lactation in ruminants (Campbell and Fell, 1970). The magnitude of this response and the relation between hepatic protein metabolism and dietary and endocrine factors remain to be studied.

Regulation of Metabolic Adaptations During the Periparturient Period

Earlier sections have identified a number of periparturient metabolic adaptations in tissues other than the gravid uterus or lactating mammary gland. These adaptations are generally initiated in late pregnancy and amplified at or soon after parturition. They are evident in numerous tissues but are best documented in adipose tissue and liver. The regulation of these major metabolic alterations will be considered in terms of the concepts of homeostasis and homeorhesis as proposed by Bauman and Currie (1980) and embellished in subsequent reviews on regulation of nutrient partitioning during pregnancy and lactation (e.g., Bauman and Elliot, 1983; Bell and Bauman, 1994). Most emphasis will be given to the regulation of lipogenesis and lipolysis in adipose tissue because of the importance of fat mobilization during the transition period and the relative abundance of illustrative data on this topic. A major conceptual theme will be the mediation of homeorhetic control through altered tissue responses to homeostatic regulators, such as insulin and adrenergic agents.

Altered Responses to Insulin and Adrenergic Effectors

Tissue responses to hormones such as insulin, glucagon, the catecholamines, and other agents of metabolic homeostasis may be classified in terms of responsiveness and sensitivity (Kahn, 1978). Responsiveness is defined as the maximal response ($\mathbf{R_{max}}$) to a given hormone, and sensitivity is defined as the hormone concentration required to produce a half-maximal response ($\mathbf{ED_{50}}$). The terms R_{max} and ED_{50} are analogous to V_{max} and K_m as applied to enzyme kinetics. Kahn (1978) considered R_{max} to be an index

of postreceptor metabolic capacity, and ED_{50} to represent an index of receptor function (number and[or] binding affinity). The degree to which changes in ED_{50} can be strictly interpreted as indicating changes in receptor function is arguable; they might equally involve alterations in early postreceptor signal transduction. Also, R_{max} could theoretically be affected by receptor number in the unlikely event that all receptors were available to bind ligand (hormone). Nevertheless, when applied carefully, the terms responsiveness and sensitivity can be used to infer mechanisms for altered cellular responses from in vivo measurements.

Responses to Insulin. We have recently shown that the insulin resistance previously observed during late pregnancy in humans and laboratory animals (Leturque et al., 1987) also occurs in sheep (Petterson et al., 1993, 1994). This is manifested as diminished sensitivity to insulin of several parameters of whole-body glucose utilization (Petterson et al., 1993) and decreased insulin responsiveness of lipolysis and NEFA mobilization (Petterson et al., 1994). Some of these results are shown in Figure 4. Altered glucose utilization probably involves adipose tissue, albeit not exclusively, because although glucose is not an important carbon precursor for fatty acid synthesis in ruminants, it is specifically required for glycerol-3-P synthesis and fatty acid esterification, and for part of the NADPH needed for fatty acid synthesis (Bauman, 1976; Vernon, 1981). Changes in responses of plasma NEFA and glycerol concentrations to insulin are likely to represent the adipose-specific phenomena of fatty acid release and lipolysis, respectively. Thus, in sheep, and probably in cattle, fat mobilization during late pregnancy is facilitated by the decreased ability of insulin to promote lipogenesis and oppose lipolysis.

The almost total suppression of adipose lipogenesis after the onset of lactation in sheep (Vernon et al., 1981a) and cows (McNamara and Hillers, 1986) is associated with low levels of plasma insulin (Hart et al., 1978) and almost complete loss of adipose responsiveness to insulin in vitro, in terms of glucose or acetate utilization (Vernon and Taylor, 1988) or fatty acid synthesis (Vernon and Finley, 1988). Vernon and Finley (1988) were unable to attribute this dramatically altered response to any change in insulin binding by adipocytes, implying a postreceptor defect (Vernon and Sasaki, 1991). This interpretation is consistent with observations of diminished responsiveness (R_{max}) but not sensitivity to insulin in vivo in terms of whole-body glucose utilization in lactating vs nonlactating goats (Debras et al., 1989). In a similar study on sheep, Faulkner and Pollock (1990) found no effect on glucose metabolism, but reported a decrease in insulin-induced suppression of plasma NEFA, glycerol, and α-amino nitrogen in ewes during early lactation. Unfortunately, their range of insulin doses was not great enough to define R_{max} or ED_{50} for these responses. In another in vivo study, the ability of insulin to stimulate hindlimb uptake of glucose was clearly attenuated in lactating ewes (Vernon et al., 1990). Taken together, these three in vivo studies suggest that early lactation (2 to 4 wk postpartum) is characterized by a moderate degree of insulin resistance in adipose tissue and muscle, thereby promoting the mobilization of NEFA and amino acids and sparing of glucose. These phenomena may be most exaggerated immediately after parturition.

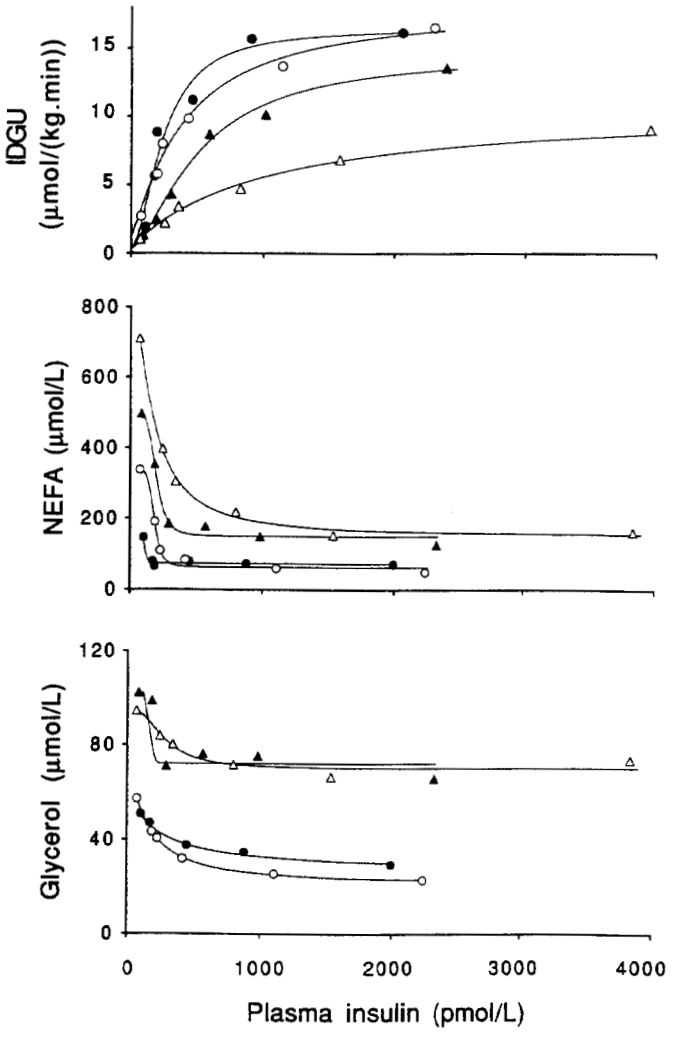

Figure 4. Effects of plasma insulin concentration under euglycemic conditions on insulin-dependent, whole-body glucose utilization (IDGU) and plasma concentrations of nonesterified fatty acids (NEFA) and glycerol in well-fed, nonpregnant (●), underfed, nonpregnant (○), well-fed, pregnant (▲), and underfed, pregnant ewes (△). Adapted from Petterson et al. (1993, 1994).

Responses to Adrenergic Effectors. Lipolytic responses in adipose tissue to adrenergic agents,

including the natural catecholamines, are markedly altered during the periparturient period. Lipolytic responsiveness and sensitivity to the β-adrenergic agonist isoproterenol were increased in adipocytes sampled from late-pregnant ewes (Guesnet et al., 1987). In a similar in vitro study, Vernon and Finley (1985) were unable to discern an effect of pregnancy on the maximal lipolytic response to norepinephrine. However, isoproterenol is a more specific lipolytic agent than norepinephrine because it binds only to adipose β-receptors and activates adenylate cyclase. In contrast, the β-mediated lipolytic action of norepinephrine may be partly masked by its additional ability to bind to α_2-receptors, which inhibits adenylate cyclase and elicits an antilipolytic response. Also, the late-pregnant ewes of Guesnet et al. (1987) were studied closer to term than those of Vernon and Finley (1985). This may be important because, in cows at least, a discernible change in lipolytic responsiveness to catecholamines does not occur until the periparturient period, as judged by in vivo responses to epinephrine injection (Bernal Santos, 1982) and in vitro responses to treatment of adipose tissue with epinephrine or norepinephrine in cows (Metz and van den Bergh, 1977; Jaster and Wegner, 1981; McNamara and Hillers, 1986; McNamara, 1988) and sheep (Vernon and Finley, 1985; Guesnet et al., 1987; Iliou and Demarne, 1987).

In vitro responses are qualitatively consistent with, but generally not as dramatic as, the increase in plasma NEFA response to i.v. injection of epinephrine in cows during early lactation vs late pregnancy (Bernal Santos, 1982). Paradoxically, the antilipolytic effect of the autocrine/paracrine factor, adenosine, on adipose tissue in vitro is also enhanced during early lactation (Iliou and Demarne, 1987; Vernon et al., 1991b). Thus, the effect of periparturient events on lipolytic capacity of adipose tissue may represent the balance between opposing actions of lipolytic (β-adrenergic agents) and antilipolytic (α-adrenergic agents, adenosine, other factors) effectors. In vitro responses to lipolytic agents may be dampened because adenosine is not as quickly metabolized and cleared as under in vivo conditions.

In addition to increased lipolytic responsiveness, the enhanced sensitivity of adipocytes to specific β-adrenergic stimulation persists into early lactation (Guesnet et al., 1987). This is consistent with observations of a substantial increase in number of β-receptors on bovine adipocytes during the periparturient period (Jaster and Wegner, 1981).

Homeorhetic Regulation of Metabolic Adaptations

General Aspects. The concept of homeorhesis as it applies to regulation of nutrient partitioning was first elaborated by Bauman and Currie (1980). They defined homeorhesis as "the orchestrated or coordinated changes in metabolism of body tissues necessary to support a [dominant] physiological state." Although not defined as such, the concept was clearly in Hammond's (1947) mind when he emphasized different tissue priorities for partitioning of circulating nutrients in farm animals during different developmental stages and physiological states. As described by Bauman and Currie (1980), key features of homeorhetic regulation are its chronic nature (i.e., hours or days vs the seconds or minutes required for most examples of homeostatic regulation); its simultaneous influence on multiple tissues with apparently unrelated functions; and its mediation through altered responses to homeostatic signals. The metabolic transition from late pregnancy to early lactation offers the clearest examples of all three of these putative features of homeorhesis.

First, most of the metabolic adaptations described in preceding sections, such as enhanced fatty acid mobilization, are initiated in late pregnancy, days or even weeks before the major increase in nutrient demand that attends the onset of lactation. Second, many of the endocrine changes that are believed to initiate and sustain lactogenesis (Tucker, 1985; Figure 5) are thought to have additional key roles in functions as diverse as the initiation of parturition and altered nutrient metabolism in adipose tissue, liver, and skeletal muscle. Third, there is emerging evidence that the altered tissue responses to insulin and adrenergic agents, described in the preceding section, are effected by the actions of putative homeorhetic hormones such as estradiol, prolactin, and, most notably, somatotropin. Observed actions of these hormones will serve as examples.

Estradiol. Plasma levels of estradiol-17β in dairy cows rise progressively through late pregnancy, peaking 1 to 2 wk before term (Figure 5). This event has been implicated in the inappetence of ruminants during late pregnancy (Forbes, 1986). It may also influence the increased propensity for fatty acid mobilization from adipose tissue during late pregnancy, independent of any change in feed intake and energy balance. Such a phenomenon has been implicated in the etiology of fatty liver in dairy cows (Grummer et al., 1990). We also have preliminary evidence that chronic treatment of nonpregnant, ovariectomized ewes with estradiol-17β, sufficient to increase plasma levels to those of near-term pregnant ewes, causes increases in plasma NEFA and glycerol consistent with those observed during late pregnancy (J. L. Andriguetto and A. W. Bell, unpublished data). It is not yet clear whether these apparent increases in lipolysis and fatty acid mobilization involve altered adipose responses to insulin or adrenergic agents. However, similar treatment of ewes with estradiol caused a major inhibition of in vitro capacity for adipose lipogenesis and fatty acid esterification (Green et al., 1992).

Prolactin. The pronounced preparturient surge in plasma prolactin (Figure 5) may also modify metabolic responses to homeostatic signals in adipose and

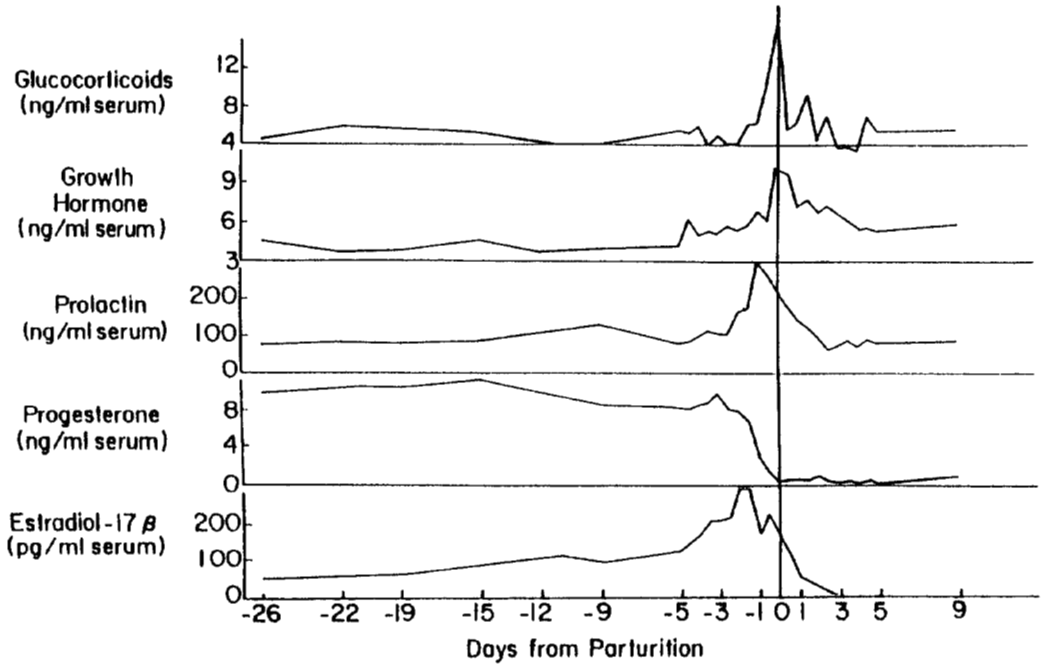

Figure 5. Changes in serum concentrations of putative homeorhetic hormones in cows during the periparturient period. Adapted from Tucker (1985).

other nonmammary tissues. In the lactating rat, reciprocal regulation of lipid metabolism in adipose and mammary tissues seems to involve prolactin-induced inhibition of insulin actions in adipose tissue and the opposite in mammary gland (see review, Williamson and Lund, 1994). Prolactin may also influence the partition of absorbed amino acids between liver and extrahepatic tissues (Garcia de la Asuncion et al., 1994). If prolactin has a role in metabolic homeorhesis in ruminants, it is likely to be more apparent during lactogenesis than during established lactation. However, despite considerable speculation (e.g., Bauman and Elliot, 1983), a role for prolactin in the coordination of preparturient metabolic adaptations with lactogenesis remains to be seriously investigated.

Somatotropin. Plasma concentrations of somatotropin (growth hormone) also rise during late pregnancy, with a marked peak at parturition and a postparturient decline to moderately elevated levels through early lactation (Figure 5). In ruminants, somatotropin rather than prolactin exerts a powerful galactopoietic influence after lactation is established (Bauman and Elliot, 1983; Bauman and Vernon, 1993). This hormone also fulfills all the criteria established earlier for a homeorhetic regulator, in terms of response time, multiplicity of actions on different functions within and between tissues and organ systems, and mediation of effects through altered tissue responses to homeostatic agents. Evidence for the regulatory actions of somatotropin and their relation to lactation performance in dairy cows has been recently reviewed (Bauman and Vernon, 1993). In the present context, it is especially notable that many changes in tissue metabolism of lactating cows treated with somatotropin seem to be mediated by altered tissue responses to insulin and catecholamines that are very similar to those observed during the periparturient period. This, together with its natural pattern of secretion, is persuasive circumstantial evidence that somatotropin is a primary homeorhetic regulator during the transition from pregnancy to lactation. Selected examples follow.

In vivo treatment with somatotropin decreases rates of lipogenesis and activities of key lipogenic enzymes in adipose tissue, apparently by opposing tissue responses to insulin (Bauman and Vernon, 1993). These actions are direct because they can be mimicked in vitro by chronic culture of adipose tissue with somatotropin. Impairment of insulin's ability to activate the key regulatory enzyme, acetyl CoA carboxylase, may be particularly important (Vernon et al., 1991a). Thus, the minimal rates of adipose lipogenesis during the periparturient period (McNamara and Hillers, 1986) are probably effected by the insulin-antagonistic influence of high circulating levels of somatotropin, assisted by low levels of insulin (Hart et al., 1978).

Somatotropin treatment also has a profound positive effect on adipose lipolytic responses to adrenergic agents in vivo, similar to that observed in the postpartum cow (Bernal Santos, 1982). Chronic treatment of lactating cows with somatotropin caused a dramatic increase in lipolytic responsiveness but did

not affect sensitivity to epinephrine, as judged from dose-response profiles of plasma NEFA and glycerol (Sechen et al., 1990). Culture of ovine adipose tissue with somatotropin for 48 h increased not only the maximal lipolytic effect of isoproterenol but also sensitivity to this β-adrenergic agonist, consistent with a concomitant increase in number of β-receptors (Watt et al., 1991). Somatotropin may also enhance adipose responses to adrenergic stimulation by opposing the endogenous antilipolytic effects of adenosine (Vernon et al., 1991b).

Treatment of cattle with somatotropin or its natural secretogogue, growth hormone-releasing factor (GRF), also affects several aspects of liver metabolism in a manner consistent with observed or likely changes in dairy cows during the transition period. First, in vivo treatment of dairy cows with somatotropin causes increased hepatic gluconeogenesis in vivo (Cohick et al., 1989) and in vitro (Pocius and Herbein, 1986; Knapp et al., 1992), possibly via a decreased ability of insulin to inhibit gluconeogenesis (Boisclair et al., 1989). Second, treatment of beef steers with GRF decreases the uptake of α-amino N and output of urea by the liver (Reynolds et al., 1992), consistent with lactation-induced changes in hepatic amino acid metabolism in the rat (Garcia de la Asuncion et al., 1994). Third, treatment of beef steers with somatotropin increases the rate of hepatic protein deposition (Early et al., 1990).

Somatotropin treatment of growing steers promotes whole-body nitrogen retention and protein synthesis in hindlimb (predominantly muscle) tissues (Boisclair et al., 1994). Clearly, these responses are at odds with observed or predicted changes in nitrogen balance and muscle metabolism in the periparturient cow. Mechanisms to explain this seeming paradox have not been studied. However, it might be hypothesized that in the mature cow, the capacity for anabolic responses to somatotropin in skeletal tissues is small relative to that in the tissue with major priority for nutrients, the mammary gland. In muscle, at least, this might be related to a developmental decline in IGF receptor abundance, as observed in the pig (Lee et al., 1993). Also, the periparturient surge in cortisol secretion (Figure 5), coupled with hypoinsulinemia (Hart et al., 1978), would not favor amino acid uptake and protein synthesis in skeletal muscle.

Conclusions

The onset of lactation in the high-yielding dairy cow imposes dramatic increases in requirements for glucose, amino acids, and fatty acids that cannot be met by dietary intake. Shortfalls in availability of these nutrients must be made up by major adaptations in adipose tissue, liver, and skeletal muscle. Most notable among these are the almost total suppression of lipogenesis and enhancement of lipolytic responses in adipose tissue, leading to a marked increase in fatty acid mobilization, and a major increase in hepatic gluconeogenesis. The latter must be supported by increased mobilization of amino acids from skeletal muscle, although this has not yet been directly documented in dairy cows. Homeorhetic regulation of these profound metabolic adjustments is indicated by their initiation in late pregnancy, well before the major increase in nutrient demand; their coordination with the first phase of lactogenesis, apparently by preparturient hormonal changes; and their amplification by the endocrine milieu that signals or attends the onset of both parturition and copious milk secretion.

Implications

This review has highlighted the quantitative discrepancy between dietary supply and mammary demand for specific key nutrients during the early postpartum period, and likely mechanisms for hormonal regulation of necessary metabolic adaptations in nonmammary tissues. Some of the hormones involved in metabolic regulation are likely to directly or indirectly affect feed intake during the closeup and early postpartum periods. Resulting changes in nutrient balance will alter the magnitude but not the pattern of nonmammary metabolic adjustments. Future research should consider why it is that relations between body condition, feed intake, and postpartum health and performance vary so widely among individual cows. Presumably, the answer will involve individual differences in capacity for homeorhetic regulation of nutrient partitioning, as observed, for example, among cows during established lactation.

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