

Partitioning of Nutrients During Pregnancy and Lactation: A Review of Mechanisms Involving Homeostasis and Homeorhesis

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ABSTRACT

Control of metabolism during pregnancy and lactation involves two types of regulation—homeostasis and homeorhesis. Homeostatic control involves maintenance of physiological equilibrium or constancy of environmental conditions within the animal. Homeorhesis is the orchestrated or coordinated control in metabolism of body tissues necessary to support a physiological state. Regulation of nutrient partitioning during pregnancy involves homeorhetic controls arising from the conceptus. This assures growth of the conceptus (fetus and fetal membranes) and gravid uterus as well as development of the mammary gland. With the onset of lactation many—perhaps even most—maternal tissues undergo further adaptations to support lactation. The coordinated adaptations in rates of lipogenesis and lipolysis in adipose tissue are examples of important homeorhetic controls of nutrient partitioning that are necessary to supply mammary needs for milk synthesis. The interactions between homeorhesis and homeostasis during pregnancy and lactation and possible endocrine control are discussed. While not definitively established, roles for placental lactogen and prolactin are attractive possibilities in homeorhetic regulation of maternal tissues to support pregnancy and the initiation of lactation, respectively.

INTRODUCTION

Lavoisier was the first to suggest that "life is a chemical process" (65). We now know that sustenance involves a series of chemical reac-

tions and physiological processes in which food is transformed into body tissues and activities. In a broad sense the chemistry of life can be considered a cycle (Figure 1). Food is consumed, and, following digestion in the gut, nutrients are absorbed. These nutrients are utilized by body tissues and, in turn through several possible mechanisms, play a role in regulating food intake (4), thus completing the cycle. In mammals, nutrients are utilized by tissues involved in maintenance and growth and for establishing body reserves including energy stores (lipids), glucose reserves (glycogen), and amino acid reserves (labile protein).

Two additional tissues utilizing a substantial portion of maternal nutrients are the developing fetus and the lactating mammary gland. One should not underestimate the importance of partitioning nutrients to support pregnancy and lactation, because these physiological states are the essence of survival of the species and, of course, the foundation of the dairy industry. However, these tissues differ from other body tissues in that they confer no special advantage to the animal. Instead, they make tremendous demands such that the total metabolism of the pregnant or lactating animal must be altered to accommodate these needs. The inability to adjust metabolism quickly enough to meet these needs frequently results in acute and subclinical metabolic disorders in farm animals. Nature has accorded a high priority to the functions of pregnancy and milk secretion, allowing them to proceed at the expense of other metabolic processes even to the point that a disease state is created.

The partitioning of nutrients to various body tissues involves two types of regulation, homeostasis and homeorhesis. Homeostatic control involves maintenance of physiological equilibrium or constant conditions in the internal environment (Figure 2). There are many well established examples of homeostasis, such as regulation to maintain constancy of body

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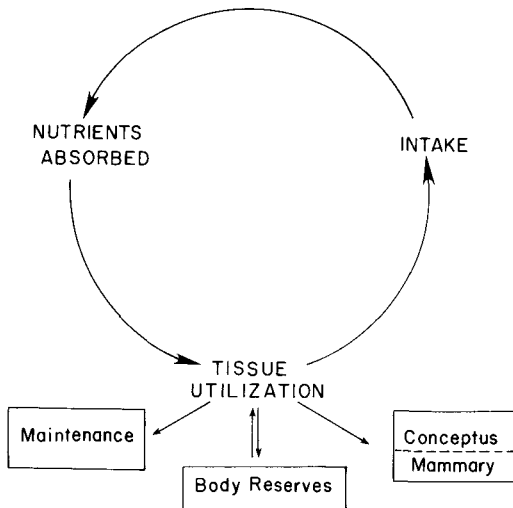


Figure 1. Cycle of life.

temperature (55). An example in metabolism deals with intake of food and partitioning of nutrients during absorptive and postabsorptive periods (94). Consumption of a meal in non-ruminants results in changes in concentrations of blood metabolites and an increase in the ratio of insulin to glucagon. These changes result in a greater uptake of glucose by liver (for glycogen synthesis) and by adipose tissue (for lipid synthesis). During the postabsorptive period, when the uptake of nutrients has diminished, the ratio of insulin to glucagon decreases sufficiently to cause glycogen and lipid stores to be mobilized. Thus, a constant supply of nutrients to peripheral body tissues is maintained by promoting short-term storage of nutrients following a meal and mobilization of these nutrients during the postabsorptive period.

Homeorhesis is the second type of control in partitioning nutrients. We define homeorhesis as the orchestrated or coordinated changes in metabolism of body tissues necessary to support a physiological state (Figure 2). The Greek derivation of homeorhesis is "uniform-flow". Hence, this is consistent with our definition, since homeorhetic regulation involves a coordination of metabolism to insure a uniform flow of nutrients in support of a physiological state. An alternative word that would be equally appropriate is the term "teleorhesis". The

Greek derivation of teleorhesis is "directed-flow". We chose to use homeorhesis since it has been used by Kennedy (55), while the term teleorhesis has not been used previously.

Perhaps the most pronounced example of homeorhesis would be in a dairy cow where initiation of lactation dramatically alters metabolism of many maternal organs in order that the mammary gland be supplied with nutrients necessary for synthesis of milk. Our review is the first to apply homeorhesis to coordinated changes during pregnancy and lactation and to emphasize implications of homeorhetic regulation in partitioning of nutrients. The broad concept, however, was noted in 1880 by Miescher (70) in that salmon virtually starved during their migration up the Rhine River, yet genital organs of the male and female developed extensively during this period, and this was at the expense of body muscles which decreased up to 55% in weight. The classic work of Hammond (42) was in reality dealing with homeorhesis when he emphasized different tissue priorities in partitioning of circulating nutrients in farm animals. Kennedy (55) introduced the term homeorhesis incidentally in his review on the thermoregulation of intake. His illustration depicted homeorhesis as the "tendency to home on to a direction or pathway of change" (i.e., partitioning of nutrients to muscle during physiological state of growth), whereas homeostasis was defined as maintenance of equilibrium within a physiological state (i.e., thermoregulation of intake).

We will discuss maternal-conceptus interactions in partitioning of nutrients and relate these interactions to possible homeostatic and

HOMEOSTASIS – Maintenance of physiological equilibrium, *i.e.* constant conditions in the internal environment.

HOMEORHESIS – Orchestrated changes for the priorities of a physiological state, *i.e.* coordination of metabolism in various tissues to support a physiological state.

Figure 2. Types of regulation in partitioning of nutrients to various body tissues.

homeorhetic controls. Although this review deals with the physiological states of pregnancy and lactation, the same concepts apply equally to the other important aspect of animal production, the physiologic process of growth.

NUTRIENT PARTITIONING DURING PREGNANCY

Pregnancy imposes a substantial cost to the animal, because total requirements for nutrients at the end of pregnancy are about 75% greater than in a nonpregnant animal of the same weight. Striking maternal adaptations are required to meet these metabolic requirements and are achieved by regulatory influences arising in the conceptus. Thus, in keeping with our concept of directed partitioning of nutrients, needs of the conceptus are accorded high priority by the homeorhetic controls it transmits to the dam. We emphasize that imposition of pregnancy includes not only development of the fetus but, in addition, growth of fetal membranes, gravid uterus, and mammary gland.

The apparent efficiency of use of metabolizable energy is exceedingly low (10 to 25%) for pregnancy in sheep (40, 80) and cattle (15, 72). This apparent inefficiency stems from ignoring the sizeable cost of maintenance of products of conception (80) and that fetal growth and development are energetically of comparable efficiency to other productive processes. A mass growth curve for the bovine fetus (Figure 3) illustrates that the bulk of accumulation of fetal mass occurs late in pregnancy when cattle are in the dry period. Hence, little competition exists between nutrient use for lactation and the major phase of fetal growth. The fetus had acquired approximately 40% of its birth weight during the first 7 mo of gestation as indicated by the dotted lines in Figure 3. During the last 2 mo of gestation fetal demands for specific nutrients (glucose and amino acids) are equal to mammary use of nutrients equivalent to about 3 to 6 kg milk/day. Various studies on differential persistency of pregnant versus open cows have indicated differences in daily production of this order at about 300 days of lactation (75). From the growth curve of Figure 3, competition by the fetus for nutrients that otherwise would be used for lactation or

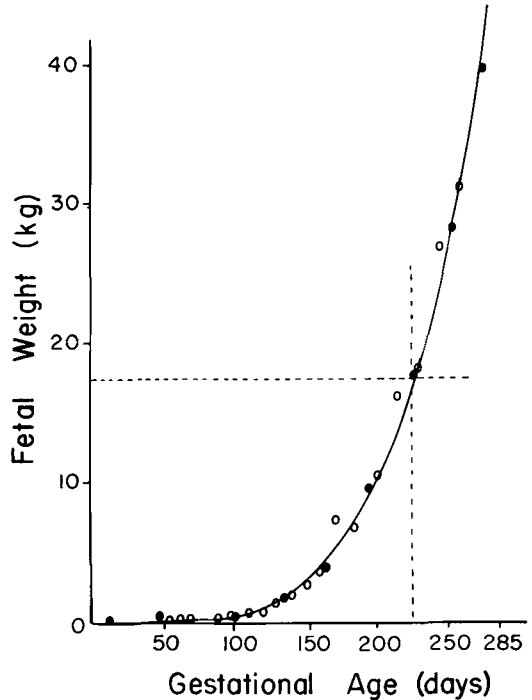


Figure 3. Growth profile of bovine fetus during pregnancy. Dotted line indicates the time when previous lactation would be terminated if the dam is given a 60-day dry period. Data shown by symbols [●] and [○] from Swett et al. (92) and Winters et al. (101), respectively.

maternal replenishment of protein and energy reserves would be increasingly important if drying off were delayed to less than 60 days before expected calving.

An understanding of the subtle differences in the nature or form of specific nutrients used in the processes of pregnancy aids in understanding maternal-conceptus interactions. Battaglia and Meschia (9) reviewed the available data indicating that umbilical uptake of oxygen by fetal sheep, goats, and cattle is of the order of 7 to 9 ml/min per kg fetal weight. If oxidative metabolism consumes primarily carbohydrates and amino acids, approximately 56 kcal/day per kg is consumed for a "maintenance-type" process. Gross energy accumulation in the conceptus unit amounts to an additional 32 kcal/day per kg in the fetus in late pregnancy. Thus, of a total of 88 kcal/day per kg, some 63% of this caloric requirement would be dissipated as heat. Comparable

calculations for cattle in late pregnancy yield 2.3 Mcal/day consumed in oxidative metabolism while about 1 Mcal/day is accumulated in the fetus. The metabolic cost of maintaining the fetus is high.

A thermal gradient of approximately .5 to 1.0°C is maintained between the fetus and dam and heat loss from the fetus (1) is comparable to that indicated previously. The relative hyperthyroidism of the ruminant fetus compared to the dam (reviewed in reference 96) might be the underlying cause of the elevated metabolic rate, and we are tempted to postulate that the actively maintained fetal hyperthermia might confer some special advantage to the fetus. It is achieved at considerable cost to the pregnant animal, because the prime substrates for oxidative metabolism appear to be glucose, amino acids, and lactate.

Data on specific nutrient requirements of the bovine fetus are limited. However, metabolism in the bovine fetus appears similar to the extensively studied ovine fetus (9). Gross uptake of carbon by the sheep fetus is about 8 g/day per kg fetal weight, of which 40% is retained, the remainder leaving as carbon dioxide and urea carbon. Glucose comprises 50 to 70% of total substrates oxidized by the fetus with 20 to 25% contributed by lactate, presumably derived from placental anaerobic glycolysis of maternal glucose (Figure 4). Amino acids provide the remaining major metabolic fuel, since fetal uptake of 1.5 g nitrogen/kg per day is grossly in excess of .65 g nitrogen/kg per day accumulated in the fetus. A substantial excretion rate of urea (.3 g nitrogen/kg per day) indicates amino acid catabolism, presumably via gluconeogenic pathways in the fetus or placenta (Figure 4). Upon prolonged fasting, amino acid catabolism within the conceptus may increase to provide 70% of turnover of fetal glucose. Despite ready availability, acetate contributes only a minor portion of the carbon oxidized to carbon dioxide. Fructose is in substantial amounts in the fetus but seems of little significance under conditions of normal maternal feeding. It has been suggested that fructose may be a form of fetal carbohydrate storage that can be utilized during fasting (9). Similarly, long-chain free fatty acids, which are transported to the fetus to provide essential fatty acids, furnish negligible quantities of energy based on radioactive carbon transfer and

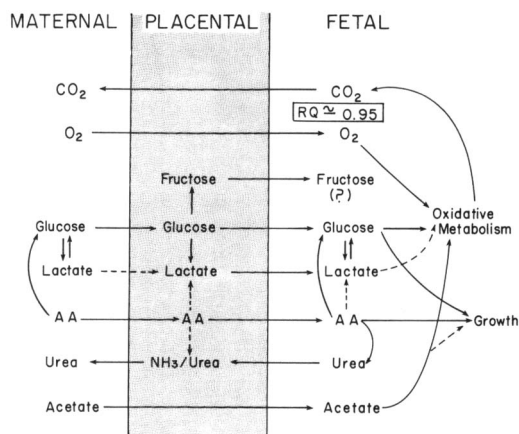


Figure 4. Overview of metabolite utilization by the ruminant fetus.

on oxygen consumption (9).

As summarized in Figure 4, fetal needs of oxidative metabolism seem to be met from the combined use of glucose, lactate, and amino acids. Since these substrates, along with others, also are used for fetal anabolism, their fate must be regulated internally in the fetus. We now are aware of the degree of fetal autonomy and that the fetus cannot be regarded as merely a "passenger". The ruminant fetus is more vulnerable than that of many species to vagaries in maternal nutrition, and severe growth retardation can result from chronic maternal underfeeding (36). Because fetal substrates are derived ultimately from the dam, their provision is buffered by the maternal system. Thus, maternal adaptations to meet fetal needs are most critical and in turn are expected to be regulated by homeorhetic signals from the conceptus. Use of substrates by the fetus seem to be determined on an acute basis by essentially homeostatic mechanisms operating within the fetus itself. Space limitation precludes our reviewing recent progress in understanding metabolic endocrinology within the fetal ruminant, and the reader is referred to reviews (7, 8, 85).

Information is scant on the biochemical potential of fetal ruminant tissues (see review 5), but what is known supports our view that fetal metabolism is characterized by an adaptation to a chronic state of hypoglycemia with impressive flexibility to redirect the use of

nutrients to sustain the necessary high metabolic rate. Thus, while glucose uptake normally might provide 50 to 70% of the requirements for fetal oxidative metabolism, this is halved within 2 days of maternal starvation and maintained there until the dam is moribund. We already have noted how amino acids are directed primarily toward a catabolic fate within the fetus to maintain energy homeostasis.

Mammary development is an often overlooked component of the metabolic burden of pregnancy. Data in Figure 5 show that the extent of mammary growth is most pronounced at precisely the period of pregnancy in which the conceptus is growing rapidly and making maximal demands of the dam. The data also show how fetal (conceptus) number exerts an influence over mammary development, probably mediated by the secretion of placental lactogen (31, 49). These prepartum events are presumably the underlying reason for lactation performance being causally related to litter size (49). The special information included in the data of Rattray et al. (81) is the strong inter-

action between fetal number and nutrition in determining mammary growth in late pregnancy (Figure 5). When ewes were fed less than requirements ($1.5 \times$ maintenance), mammary growth was decreased, but the effect of fetal numbers was still apparent. There appears to be an "anticipatory" signal, emanating from the conceptus, which is the first component of the homeorhetic control preparing the dam for lactation. Nutrient availability, however, dictates whether the influence of the conceptus is expressed fully. During pregnancy the flow of nutrients across the placenta and into the developing mammary gland are both under control of hormones from the conceptus. The loss of nutrients confers no advantage whatsoever to the dam, and as exemplified by the sheep with pregnancy ketonemia, the high priority accorded the nutrient demands of the fetus may compromise severely the metabolic integrity of the animal. While teleologically appropriate, the fetal homeorhetic influence contributing to mammogenesis is remarkable, because benefits accrued are not realized until after birth when the young requires milk.

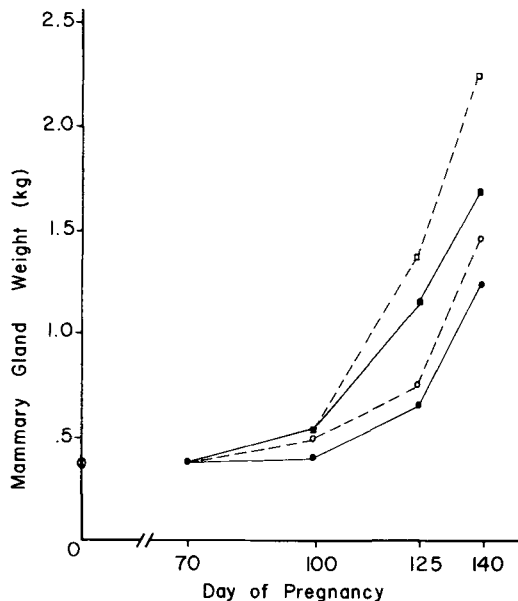


Figure 5. Growth of sheep mammary gland during pregnancy as related to fetus number and intake. Ewes with a single fetus are indicated by circles while those with multiple fetuses are indicated by squares. Ewes were fed either $1.5 \times$ maintenance (solid line) or $2.0 \times$ maintenance (dashed line). Data from Rattray et al. (81).

NUTRIENT PARTITIONING DURING LACTOGENESIS

The functional mammary gland is one of the most highly differentiated and metabolically active tissues in the body (30). The period of lactation in which the animal's ability to coordinate partitioning of nutrients assumes the most critical role is during the onset and development of copious milk secretion. At the initiation of lactation, marked alterations in the general partitioning of nutrients and metabolism of the whole animal must occur to accommodate demands of the mammary gland. As previously indicated, maternal tissues have adapted to meet fetal needs during pregnancy, but these adaptations become even more pronounced in support of lactation. The nutrient needs of the mammary gland are of such magnitude relative to total metabolism in a high producing dairy cow that the cow should be considered an appendage on the udder rather than the reverse (19).

Presented in Figure 6 is a partial listing of metabolic changes which occur with initiation of lactation. One of the major changes, which will be discussed in detail, occurs in adipose

Physiological Function	Metabolic Change	Tissues Involved
Milk Synthesis	Increased use of nutrients	Mammary
Lipid Metabolism	Increased lipolysis Decreased lipogenesis	Adipose tissue
Glucose Metabolism	Increased gluconeogenesis Increased glycogenolysis	
	Decreased use of glucose and increased use of lipid as energy source	Body tissues in general
Protein Metabolism	Mobilization of protein reserves	Muscle and other body tissue
Mineral Metabolism	Increased absorption and mobilization of calcium	Kidney, liver, gut and bone

Figure 6. A partial list of the metabolic changes associated with lactogenesis in ruminants.

tissue; here uptake of nutrients for synthesis of storage lipids is decreased, and lipid reserves are mobilized instead. Another key nutrient is glucose, and the maximally secreting mammary gland may require up to 80% of the total glucose turnover. A coordinated response meets this need; rates of gluconeogenesis in the liver are increased dramatically, and presumably glycogen is mobilized. A portion of the increase in liver gluconeogenic rates is from the increased intake when lactation commences (61), but total glucose synthesized per day increases even if a constant intake is maintained (13). The preference of other body tissues for nutrients to be oxidized for energy also is altered to allow partitioning of a greater percentage of glucose to the mammary gland. At day 30 prepartum, 34% of the total glucose turnover is oxidized to CO_2 , whereas this decreases to only 8 to 9% by day 7 of lactation (13). Nitrogen balance studies have demonstrated the importance of labile protein reserves in meeting amino acid needs for milk protein and glucose synthesis in early lactation. These reserves are substantial and may comprise 25 to 27% of total body protein in a dairy cow (18).

Mineral metabolism is another area with extensive changes at onset of lactation (Figure 6). DeLuca and Schnoes (32) have reviewed the system by which calcium metabolism is regulated via vitamin D. The mechanism involves liver, which converts vitamin D_3 to 25-hydroxyvitamin D_3 , and kidney, which forms 1α , 25-dihydroxyvitamin D_3 . This is the active form of vitamin D that stimulates intestinal calcium transport, mobilization of calcium from the bone, and renal reabsorption of

calcium. While this model for eucalcemia has evolved from studies with laboratory animals and avian species, it seems likely that a similar system must be involved to meet mammary demands in a dairy cow (41).

The listing in Figure 6 is by no means complete, and many other important maternal functions also adapt to support lactation. Rather, the list is intended to underline that lactation is not just a function of the mammary gland. Commencement and maintenance of a successful lactation are dependent on alterations in many, perhaps even most, maternal tissues such that nutrients are partitioned to the mammary gland. Thus, regulation of nutrient partitioning by homeorhetic and homeostatic mechanisms is extremely important in insuring a high rate of milk production.

Lipid Metabolism

We have chosen to consider in depth the coordination of tissues associated with energy availability for two reasons. First, of the major nutrients, changes in the partitioning of metabolites associated with energy are probably of the greatest magnitude with onset of lactation. Second, if the animal is unable to alter energy metabolism rapidly or to the extent needed to meet demands for milk synthesis, either the cow produces well below her capability or she is susceptible to various metabolic disorders and health problems.

The importance of altered partitioning of nutrients is indicated by considering the energy status of high producing cows as in Figure 7. These averages were calculated from the data of Moe (71) with high producing cows having a full lactation. Milk yield (4% fat-corrected to equalize energy content) peaked in wk 3 to 4 of lactation, whereas net energy intake (calculated by 1978 standards (73)) did not peak until several weeks later. During the first one-third of lactation, cows were in a negative energy balance and were using body energy reserves to meet their needs (Figure 7). In fact, a zero net energy balance (i.e., intake sufficient to meet requirements) was not achieved until a point in lactation where milk production had decreased to less than 80% of peak production. During the first 10 wk of lactation the net energy deficit of these cows was energetically equivalent to approximately 50 kg pure lipid or an

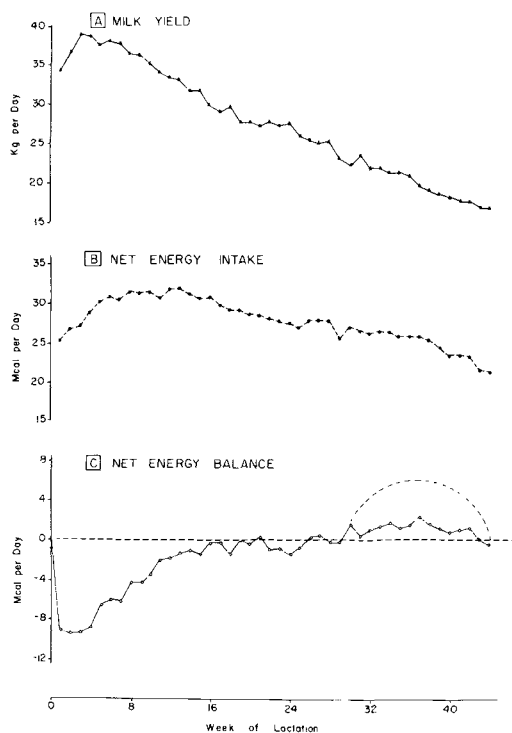


Figure 7. Relationship between energy intake and requirements for a lactation in high producing dairy cows. The six cows averaged 9,534 kg milk and 332 kg fat for the 305-day lactation. Milk yield [A] is kg/day of 4% fat-corrected milk, net energy intake [B] as Mcal/day, and calculated net energy balance [C] as Mcal/day. Cows were from the data of Moe (71) and net energy requirements and feed values from National Research Council (73). Dashed line [panel C] indicates recommended overfeeding during last one-third of lactation to replenish body energy stores needed to support the next lactation.

average daily production of 9 kg milk. Even more impressive, during the first month of lactation the body reserves being utilized (i.e., net energy deficit) were energetically equivalent to about 33% of the milk produced. Under normal management conditions, the dairy cow is overfed during the last one-third of lactation to replenish body energy stores in preparation for the next lactation. This is indicated by our dashed line in Figure 7. The study by Moe (71) was designed to examine energy requirements for milk production and maintenance; hence, these particular cows were fed to maintain body weight during the last half of lactation.

Body energy reserves are predominantly in

the form of lipids stored in adipose tissue. The adipocyte has only two major functions—synthesis of lipids and mobilization of lipids. Details of biochemical pathways in adipose tissue have been reviewed (10, 12) and are in schematic form in Figure 8. The left side of the cycle involves lipid synthesis and includes de novo synthesis of fatty acids from acetate, uptake of fatty acids from circulating lipoproteins via the enzyme lipoprotein lipase, and esterification of these fatty acids into triglycerides (the storage form of lipid). The right side of the cycle depicts lipolysis or mobilization of fatty acids. Lipid synthesis and mobilization tend to be reciprocal processes in the adipocyte. Thus, regulation of these two biochemical processes is coordinated, and factors which directly effect one process tend to cause a reciprocal change in the other process either via direct or indirect action (10, 12).

The temporal relationship between metabolism of adipose tissue and onset of lactation has been studied most extensively in the rat. At about day 19 of pregnancy, lipoprotein lipase activity in adipose tissue decreases (43, 57), and both flux rates and activities of key enzymes in the regulation of de novo fatty acid synthesis begin decreasing rapidly (37, 59, 66). The net effect is that energy storage in adipose tissue is diminished. Consistent with the reciprocal relationship between synthesis and mobilization, rates of lipolysis are increased markedly during this time as evidenced by adipocyte metabolism and/or concentrations of free fatty acids in

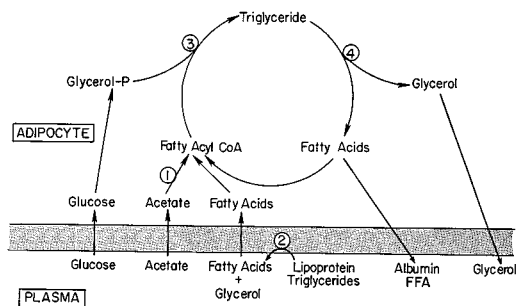


Figure 8. Overview of lipid synthesis/mobilization cycle in ruminant adipose tissue. Depicted are 1) de novo fatty acid synthesis; 2) uptake of preformed fatty acids from circulation; 3) fatty acid esterification and 4) fatty acid mobilization. Figure adapted from Bauman (10).

blood (59, 66). Thus, during this transition in physiological state, metabolism of adipose tissue has altered in such a manner as to support partitioning of nutrients to mammary glands for synthesis of milk. The impressive aspect of these changes is that they occur several days prior to birth of the young. Therefore, it is not surprising that during this interval a lipemia of pregnancy occurs in the rat where both serum triglycerides and free fatty acid concentrations are elevated (57, 59, 76, 84).

Ruminants and other mammals have similar adaptations in lipid metabolism, although the temporal relationships have not been established as definitively. Chilliard and coworkers (23, 24, 25), working with goats, demonstrated that both lipoprotein lipase (necessary for the uptake of preformed fatty acids) and acetyl CoA carboxylase (a regulatory enzyme in *de novo* synthesis of fatty acids) decreased in activity in adipose tissue during late pregnancy and remained low during lactation. They emphasized a relationship between adipose and mammary metabolism based on enzyme data and positive correlation between concentrations of free fatty acids in serum and mammary metabolism (24). Investigations with cows in late pregnancy and early lactation have demonstrated the same increased rates of lipid mobilization (69, 87, 91) and decreased rates of pathways of lipid synthesis in adipose tissue (69, 86, 87). Rabbits (68), sheep (74), and humans (51) are other species in which these coordinated changes in adipose tissue metabolism and in concentrations of lipid in serum have been observed during this physiological transition.

Relationship Between Homeostasis and Homeorhesis

The coordinated, developmental changes in metabolism of adipose tissue in late pregnancy are examples of homeorhesis. Overall, the homeorhetic controls operating during lactogenesis have altered adipose tissue metabolism (decreased lipid synthesis and increased lipid mobilization) to support a new physiological state. However, homeostatic controls also are operating throughout this period to maintain equilibrium in the face of such environmental challenges as stress or daily rhythms in circulating metabolites associated with meal consumption.

The excellent study by Mertz and van den Bergh (69) illustrates the relationship between homeorhesis and homeostasis. These workers obtained biopsies of adipose tissue from dairy cows at various times around parturition and determined basal and noradrenalin-stimulated rates of lipolysis. Noradrenalin is a homeostatic regulator associated with stress and represents a lipolytic challenge to indicate maximum rates of lipolysis. As in Figure 9, during late pregnancy and early lactation, basal rates and noradrenalin-stimulated rates of lipolysis increase several fold. These changes parallel the rise in plasma concentrations of free fatty acids. The same alteration in lipolytic response to noradrenalin also has been observed with *in vivo* studies in dairy cows (87). Glucose and insulin are homeostatic regulators of lipid metabolism in adipose tissue. Consistent with the continuous need for lipid mobilization during early lactation in a dairy cow, adaptations also have occurred in adipose tissue such that lipolytic rates are unaffected by glucose during this period (69). Insulin stimulates lipogenic rates in adipose tissue under most physiological conditions, but studies with rats have demonstrated that during late pregnancy adipose tissue has diminished responsiveness to insulin (58, 59, 84). Although biochemical studies have not been done, one can envision

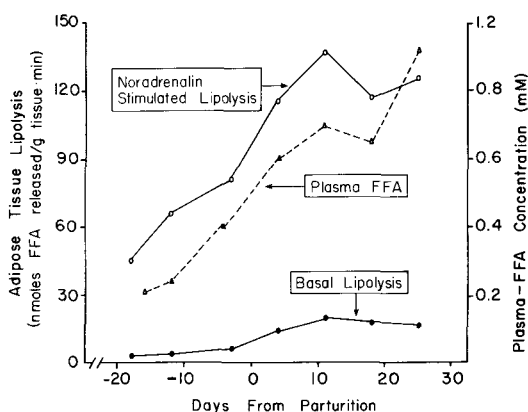


Figure 9. Adipose tissue rates of lipolysis and plasma concentrations of free fatty acids during lactogenesis in cows. Adipose tissue biopsies were obtained and incubated in presence (\circ) and absence (\bullet) of 25 μ M noradrenalin. Blood samples were obtained in the same cows for free fatty acid measurements (\triangle). Data adapted from Metz and van den Bergh (69).

that developmental adaptations, which must have occurred in response to homeorhetic signals, may be alterations in activities of key cellular enzymes (such as adenylyl cyclase) and changes in adipocyte receptors to homeostatic signals (such as the number of insulin receptors). Thus, regulation of energy metabolism and likely partitioning of most major nutrients involve a remarkable interaction between homeorhetic and homeostatic controls to insure perpetuation of the species.

There is another critical aspect of the interaction between homeorhesis and homeostasis. If an environmental challenge (such as management practice, plane of nutrition, disease, etc.) is of sufficient magnitude, homeostatic controls for survival can overwhelm homeorhetic mechanisms operating in support of a physiological function. The previously discussed relationship between intake and mammary growth during pregnancy (Figure 5) and the overfeeding of cows in late lactation to allow a build up of body fat reserves (Figure 7) are examples of this. An example that is visualized more easily is a growing animal that suddenly is starved. Even though the goal sought is growth, the lack of nutrients overwhelms homeorhetic drive such that homeostatic controls for survival become more important, and growth ceases or even reverses.

The importance of this interaction becomes evident when one considers the series of publications by Hart and coworkers (46, 47, 48) comparing a group of high-producing dairy cows with low-producing crossbred cows. Their study examines the relationship between concentrations of circulating hormones in two groups of cows with differing milk yield. They observed that concentration of growth hormone in blood was higher, whereas insulin was lower in the high producing group. Their publications (46, 47, 48) and reviews (14, 27) have emphasized that these hormones may be key endocrine factors that differ between high and low yielding cows and have discussed possible implications in inherited differences in the partitioning of nutrients to support lactation. Because intake was identical for both groups, the plane of nutrition must be considered in interpreting these data. For a typical milk composition, one can estimate the net energy balance of the two groups. At any point in lactation when blood samples were obtained

(days 40, 80, 120, and 180), the difference in net energy intake relative to requirements between the two groups was about 40 to 50%. For example at day 40 of lactation, low producers were overfed by 20 to 25% relative to requirements, whereas high producers were underfed 20 to 25%. Blood samples were obtained at times well after developmental changes in nutrient partitioning in late pregnancy and early lactation, so the comparison primarily may involve homeostatic mechanisms. However, homeostatic control was not examined under a similar situation, because comparisons were between substantially overfed cows (low-producing group) and underfed cows (high-producing group). With this study (46, 47, 48) as a base, recent investigations using only high producing dairy cows have shown that the same magnitude of differences in growth hormone and insulin occur if animals are overfed or underfed to the same degree (11, 100). Thus, implications of hormonal data in studies comparing high- and low-producing cows fed identical nutrient intakes are difficult to interpret. The interaction between homeostasis and homeorhesis must be considered adequately in studies designed to identify inherited differences in partitioning of nutrients to support a physiological state.

ENDOCRINE CONTROL OF HOMEORHESIS

In 1947, F. G. Young (102) suggested: "Growth, including foetal growth, and milk production are processes requiring a special type of metabolic control . . . it would not be surprising if there were some relationship between the hormonal mechanisms concerned with the control of these phenomena." Our knowledge of the endocrine control of nutrient partitioning to support pregnancy and lactation is still only in the infancy stage. Existing concepts are based almost entirely on subjectively relating serum hormone concentrations with metabolic events and on studies with rats as a model. We refer readers to reviews by Convey (26) and Trenkle (97) for detailed discussion of limitations associated with such studies. In particular, studies relating hormone concentrations in serum to metabolic events do not account for possible changes in blood flow to a tissue or in alterations in numbers of hormone receptors in a target tissue. In addi-

tion, serum concentrations of protein hormones are determined typically by radioimmunoassay, and we are not aware of any instance where the radioimmunoassays for ruminant protein hormones have been demonstrated to correlate with biological activity of the hormone in serum. With these limitations in mind, the remainder of this section will discuss the possible endocrine control of homeorhesis during pregnancy and initiation of lactation. Given the complexity of mammalian regulation, endocrine control of nutrient partitioning is likely to be complex with overlapping systems involving many synergisms. We will discuss only those hormones for which published investigations have proposed an involvement in what we refer to as homeorhetic control of nutrient partitioning.

Placental lactogen, secreted by the conceptus, may be involved in homeorhetic control of maternal metabolism during pregnancy. In many species, including ruminants, placental lactogen concentrations in maternal serum are high during the last one-third of pregnancy (29, 49, 54), coinciding with the period of rapid growth of the fetus (Figure 3). Placental lactogen is similar in structure to growth hormone and prolactin, and in many species and tissues it binds to the same receptors as these pituitary hormones (17, 21, 29). Mammary, adipose, and liver are among the tissues in which membrane receptors for placental lactogen have been reported (17, 21, 22, 29).

Kaplan and Grumbach (51) have proposed that placental lactogen coordinates maternal liver and adipose tissue metabolism in a manner to supply nutrients to the developing fetus. Applying the concepts of our review, placental lactogen would represent a homeorhetic control. The model of Kaplan and Grumbach (51) also includes examples of how short-term homeostatic controls would interact with homeorhesis such as alterations in insulin during meal consumption or in the postabsorptive period. While a role for placental lactogen in homeorhetic control of nutrient partitioning during pregnancy is attractive, it has by no means been established definitively. Rather, the hypothesis is based primarily on the positive relationships between concentrations of placental lactogen in maternal serum and blood concentrations of free fatty acids, number of fetuses, or birth weight of the fetus (51).

Estrogens and progesterone also may participate as homeorhetic controls of nutrient partitioning during pregnancy. Changing the estrogen to progesterone ratio alters blood supply to the uterus and, thus, could affect nutrient availability to the fetus (20). We have already pointed out that fetal development and mammary growth occur concurrently during the last third of gestation. Since coordinated responses of maternal tissues are essential to support pregnancy, it is not surprising that estrogen, progesterone, and placental lactogen all play a positive role in growth of mammary glands (see review by De Louis et al. (31)).

Most investigations of endocrine control of lactogenesis have concentrated on the mammary gland. Details regarding hormonal changes in cows during the last few days of pregnancy and the relationship of the hormones to mammary differentiation are in reviews by Thatcher et al. (95) and De Louis et al. (31). In brief, Kuhn (60) has characterized the homeorhetic control of lactogenesis as both a "release" of inhibition and a "push" to commence synthesis. Progesterone concentrations in the blood begin to decrease gradually during the last weeks of pregnancy and then decrease precipitously immediately prepartum. As a result the progesterone inhibition on mammary differentiation is released. Simultaneously, estrogens are increased in the maternal circulation, and this is followed by the prepartum surge in prolactin. Prolactin represents one of the key components of the "push" necessary for final stages of differentiation that result in mammary tissue acquiring the ability to synthesize milk components (60). A synergism may exist between estrogens and prolactin, because estrogen induces pituitary release of prolactin (67, 83) and perhaps also causes the increase in the number of prolactin receptors in mammary tissue which occurs prepartum (33, 34).

The obvious question is whether these same hormones involved in regulating mammary tissue during lactogenesis also have a role in the homeorhetic control of other maternal tissues necessary to support the commencement of lactation. A role for prolactin is attractive. The prepartum surge in prolactin corresponds reasonably well with the timing of metabolic changes in many maternal tissues. Blocking the prepartum release of prolactin in dairy cows with the drug 2-bromo- α -ergocryptine results in

a 40 to 50% reduction in subsequent milk production (3, 50), and this effect is overcome by the simultaneous administration of exogenous prolactin (3). In addition, prolactin is released as a result of suckling or a milking stimulus, and in dairy cows the magnitude of the release decreases as lactation progresses (98). This release could be nature's way to reinforce needs of the mammary gland and, hence, those of the nursing neonate.

Several investigators have proposed that prolactin coordinates lipid metabolism in adipose and liver in a manner to partition nutrients to the mammary gland (2, 66, 103). Blocking release of prolactin during lactogenesis or in early lactation produces not only the previously cited negative effect on mammary synthesis of milk but also results in an increase in adipose and liver pathways of lipid synthesis (2, 66, 103) as well as a reduction in the rates of lipid mobilization from adipose tissue (66). These investigations, with the rat as a model, further demonstrated that in mammary, adipose, and liver tissue, adaptations in lipid metabolism were reversed if exogenous prolactin was administered. Prolactin receptors have been identified in adipose tissue and liver (17, 53, 79), and liver receptor numbers increase in late pregnancy (53). Thus, the concept emerges that prolactin would be involved in homeorhetic control to support lactation needs by decreasing synthesis of lipid reserves and increasing mobilization of adipose lipid stores. Hypertrophy of the gastrointestinal tract is another maternal tissue adaptation which occurs with the onset of lactation in ruminants and laboratory animals (28, 63, 99). Prolactin has been implicated in the hypertrophy and increased absorptive capacity which occurs in the gastrointestinal tract of rats during the onset of lactation (63). A role for prolactin in regulation of calcium metabolism in avian species also has been reported (89) but apparently has not been studied in any mammalian species.

Some reservations also exist in proposing a role for prolactin in homeorhetic control of lipid metabolism during lactogenesis. It is possible that these changes in adipose tissue and liver metabolism resulting from manipulation of prolactin are not caused directly but are merely a consequence of the change in nutrient utilization by mammary tissue elicited by prolactin.

This seems unlikely, with our current knowledge of hormone receptor distribution and of developmental changes in adipose tissue that commence in late pregnancy prior to the actual demand for milk by the nursing neonate. Indeed, when one considers the critical role of a successful lactation in the perpetuation of mammals, active support of the needs of mammary tissue would be expected.

Furthermore, blocking prolactin release (via injection of specific drugs) during established lactation in dairy cows has no effect on milk production (52, 88). Several possibilities exist to reconcile this observation with the proposed role of prolactin in homeorthesis. First, endocrine signals in homeorhetic control at the onset of lactation could be different from those in maintenance of lactation. Second, the length of time over which prolactin was blocked could have been inadequate to allow for both the biochemical changes in maternal tissues to occur and the impact of repartitioning of nutrients to be manifest. Studies with goats suggest this is unlikely, because decreasing prolactin release for a period of 44 days had no effect on milk yield (44). Third, overlapping systems in endocrine control may have allowed other hormones to compensate for the absence of prolactin. In nonruminant species, blocking prolactin release during lactation results in a cessation of lactation (38, 64, 82, 93), but all investigations involved the early portion of lactation (prior to peak production), and, thus, are not comparable to studies with cows (52, 88) or goats (44) at later stages of lactation. Enhancing prolactin via exogenous administration of adequately purified hormone apparently has not been attempted in dairy cows. However, daily injection of several drugs, which apparently stimulate prolactin release with no adverse side effects, results in over a 50% increase in milk yield by lactating ewes (6).

A final reservation in the proposed role of prolactin in the homeorhetic control of lipid metabolism during the onset of lactation stems from the work of Swan (91). He also proposed that prolactin coordinates lipid metabolism but in the exact opposite manner to the work previously cited. He suggested that prolactin promotes accumulation of body lipid reserves in dairy cows based on the negative correlation between basal concentrations of prolactin and serum free fatty acids during the first 90 days

of lactation (91). However, basal concentrations of prolactin only ranged from 5 to 20 ng/ml in his study and he failed to consider implications of the dramatic prepartum surge of prolactin (>250 ng/ml) and the fact that release of prolactin at each milking (>100 ng/ml) decreases as lactation progresses (98).

The evidence for other hormones in homeorhetic control of maternal metabolism to support lactation is even less definitive. Estrogen may function in a manner analogous to its role in mammary lactogenesis. Estrogen injections increase the number of prolactin receptors in rat liver (78), and this effect is amplified or mediated by prolactin (77). Estrogen injections also reduce the activity of lipoprotein lipase in rat adipose tissue (45). Exogenous administration of prostaglandin $F_{2\alpha}$ to rats in late pregnancy results in decreased adipose tissue and increased mammary tissue activities of lipoprotein lipase (90). These reciprocal changes in lipoprotein lipase activity induced by prostaglandin $F_{2\alpha}$ are blocked by simultaneous administration of progesterone. Growth hormone also has been suggested to coordinate metabolism, particularly during the maintenance of an established lactation (14, 27). Serum concentrations of growth hormone in dairy cows do not relate temporally to metabolic changes during lactogenesis. However, that administration of growth hormone to lactating cows increases milk production (62) indicates that at least exogenous hormone can increase partitioning of nutrients to the mammary gland. Metabolic adaptations that may be occurring in dairy cows given exogenous growth hormone are discussed in the review by Bines and Hart (14).

OVERVIEW

Identifying the physiological basis of differences among animals in milk and meat production is being recognized as a high research priority for animal scientists. While this symposium deals with maternal-conceptus interactions, these same principles also should be viewed in a larger context. When considering the "chemistry of life" (Figure 1), genetic differences among animals may exist in the extent of digestion and absorption of nutrients in the gut, in the partitioning of nutrients to the various body tissues, and in the interrelationship of nutrient utilization and regula-

tion of intake. Genetic differences in partitioning and utilization of nutrients loom as a major possibility when one considers that Beecher Arlinda Ellen, holder of the world milk production record, produced 25,300 kg of milk in a 365-day lactation. Variation in regulation of nutrient partitioning could involve inherited differences in circulating hormones (i.e., extracellular signals), in cellular recognition of these signals (i.e., receptors), and cellular expression of these signals (i.e., synthesis/degradation of regulatory enzymes). Several reviews have dealt with some facets of these possibilities (16, 27, 39, 56).

Regulation of nutrient partitioning to support fetal development and subsequent milk synthesis is complex. The conceptus unit plays a critical role in assuring adequate nutrients for its development as well as for the dam's mammary development and subsequent milk production. This review has attempted to crystallize the concepts of homeorhesis and homeostasis and to integrate these two types of regulation in control of metabolism during pregnancy and lactation. Because many of the concepts we have proposed are original, perhaps it is appropriate to conclude with a comment by the late E. Duclaux, an eminent French scientist. In evaluating the scientific contributions of Louis Pasteur, Duclaux points out, "... we see clearly how much a matter of indifference it is whether a theory or a doctrine is right, provided, it incites to work, and results in the discovery of new facts" (35).

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