Homeostatic Mechanisms that Regulate Lactation during Energetic Stress\textsuperscript{1,2}

Peter E. Hartmann,\textsuperscript{3} Jillian L. Sherriff* and Leon R. Mitoulas

Department of Biochemistry, The University of Western Australia, Nedlands, WA 6907, Australia and *School of Public Health, Curtin University of Technology, Perth, WA, 6001, Australia

ABSTRACT Apart from the metabolic differences between species (ruminant vs. nonruminant), there are other important physiologic differences in both the energy requirements for lactation and in the control of milk production between dairy cows and women. Unlike dairy cows, the partitioning of nutrients for lactation in women therefore cannot be generalized to all lactating women but must be related to individual women, taking into account their particular metabolic circumstances. Homeorhetic models may be appropriate for women in developing countries, whereas in developed countries, the flexibility in both homeostatic and homeorhetic adaptations to the substrate demands for milk synthesis means that women can adopt a variety of strategies to support the metabolic demands of lactation. In these women, as in dairy cows, body reserves, dietary intake and milk production vary widely among individuals, and individual differences in capacity for homeorhetic regulation of nutrient partitioning under these conditions require further investigation. J. Nutr. 128: 394S–399S, 1998.

KEY WORDS: * energy * homeorhetic * homeostatic * humans * lactation

The foundation was laid for the investigation of the homeo-
static mechanisms that regulate lactation during energetic stress in women more than 200 years ago with the discoveries of the brilliant French scientist Antoine Lavoisier (see Prentice 1995). Although he was not the only scientist at that time to compare the amount of heat given off by an animal with that given off by a lighted candle, Lavoisier made a major breakthrough by recognizing that the vital process involved was the consumption of a new element which he named “oxy-
gene” and was not due to the production of “phlogiston.” He
and Laplace combined direct (heat loss) and indirect (gas exchange) calorimetry to show that the quantity of heat produced was directly proportional to the amount of “oxygene” consumed. Lavoisier then studied human metabolism and by 1790 had determined that “oxygene” consumption was increased by the ingestion of food, muscular work and exposure to cold. He linked together his work on chemistry and metab-
olism with the phrase “La vie est une fonction chimique.” Un-
fortunately the world was prematurely deprived of Lavoisier’s genius in 1794 when he was charged with the adulteration of tobacco with water and guillotined. Nevertheless, his investiga-
tions set the basis for our current understanding of mamma-
lian metabolism.

Although Lavoisier defined the overall process of respira-
tion by demonstrating that oxygen was consumed and heat as well as carbon dioxide were produced, he could not have imag-
ned the complexity of the intervening metabolic pathways.
Indeed, the mechanisms by which food as well as body reserves of energy are partitioned into particular anabolic processes is of considerable importance in both animal production and human nutrition. In this context, the metabolic adaptation to lactation is of particular interest. Homeostatic adjustments in lactation are influenced by milk composition, the substrates used for milk synthesis, the partitioning of nutrients between body tissues and organs, the mechanisms controlling milk syn-
thesis, the energy output in milk, the efficiency of milk syn-
thesis as well as dietary energy intake and level of physical exer-
cise.

MILK COMPOSITION

The milks of different species contain the same unique
classes of compounds, but the relative amounts of these com-
ounds vary greatly among species (Oftedal and Iverson 1995). Compared with other mammals, the composition of human milk is at one extreme. Human milk contains a very low con-
centrations of lactose (184 ± 14 mmol/L) and oligosaccharides
The rise in the fat content of milk from the beginning of lactation to established lactation is a measure of the physiologic capacity of the breast to store milk (storage capacity). The minimum fat content will occur at a fullness of 1.0 and the maximum fat content will occur at a fullness of 0.0. Because the storage capacity is an anatomical characteristic peculiar to each breast, it follows that the estimation of the average fat content as well as daily milk fat production for an infant breast-fed on demand must be based on individual measurements of the fat content and milk production for each breast. Furthermore, the results of breast expression cannot be relied upon because milk removed by breast expression (or pumping) may be required during the day at times of high rates of milk synthesis. Amino acids for milk synthesis also are supplied because milk removed by breast expression (or pumping) may be required during the day at times of high rates of milk synthesis. Amino acids for milk synthesis also are supplied to the end of a breast-feeding is determined primarily by the changes in metabolism of the body tissues necessary to support milk synthesis. Free fatty acids and lactose are synthesized from blood free amino acids and lactose is synthesized from blood glucose. The glycerol moiety of the milk triacylglycerols is derived largely from glucose in all species, whereas the shorter-chain fatty acids are synthesized in the mammary gland and derived either predominantly from acetate and \( \beta \)-hydroxybutyrate in ruminants or from glucose as well as acetate in nonruminants. The longer-chain fatty acids are transported from either the diet or adipose tissue to the mammary gland bound to blood lipoproteins for direct incorporation into milk triacylglycerols.

From a knowledge of human metabolism, it can be predicted that the substrates for breast milk synthesis are blood glucose (for lactose and shorter-chain fatty acid synthesis as well as energy required for milk synthesis), fatty acids from triacylglycerols in blood chylomicrons and VLDL (for longer-chain fatty acids), blood free amino acids (for protein synthesis) together with some contribution from lactate, acetate, glycerol, ketone bodies and FFA. When a woman derives around 30% of dietary energy from fat, the de novo synthesis of medium-chain saturated fatty acids accounts for 10–12% (by weight) of the fatty acids in milk, and the long-chain fatty acids derived from the diet contribute 29% of the fatty acids (Hachey et al. 1987). The remaining fatty acids are either synthesized in other tissues or mobilized from fat depots. Carbohydrate metabolism is dominated by the demand for glucose by the mammary gland. It is probable that most of the glucose required for milk synthesis is derived from the diet; however, glycogenolysis as well as hepatic gluconeogenesis from lactate, glycerol and amino acids may be required during the day at times of high rates of milk synthesis. Amino acids for milk synthesis also are supplied from the diet. However, "labile protein reserves" in the liver and skeletal muscle may contribute to milk synthesis when dietary intake is sparse.

**PARTITIONING OF NUTRIENTS**

Work carried out in the U.S. by Max Kleiber and his group at the University of California, Davis conceptualized overall energy metabolism in mammals and documented the link between metabolic demands of the mammary gland and the energy economy of the lactating cow. More recently, Bauman and Currie (1980) at Cornell University, Ithaca developed the concept of homeorhesis, "the orchestrated or coordinated changes in metabolism of the body tissues necessary to support a [dominant] physiological state," to explain the different tissue priorities for partitioning of circulating nutrients during different developmental stages and physiologic states such as...
pregnancy and lactation. Homeorhesis is characterized by chronic regulation (hours or days) rather than the acute regulation of homeostasis (seconds or minutes), and by simultaneous influence on multiple tissues with apparently unrelated functions; it is mediated through altered responses to homeostatic signals (Bell 1995).

Many of the metabolic adaptations to lactation are initiated in late pregnancy, usually before the enhanced nutrient demand by the fetus. These adaptations are augmented by the endocrine changes that initiate and sustain lactation by altering nutrient metabolism in adipose tissue, liver and skeletal muscle (Bell 1995). Thus in the high yielding dairy cow, dramatic increases in the requirements for glucose, amino acids and fatty acids during early lactation cannot be met by dietary intake alone; major metabolic adaptations in adipose tissue, liver and skeletal muscle make up the gap. Nevertheless, Bell (1995) observed that the relations between body condition, feed intake, and postpartum health and performance vary widely among individual cows and concluded that this may be the result of individual differences in the capacity for homeorhetic regulation of nutrient partitioning.

CONTROL OF MILK SYNTHESIS

**Endocrine.** In the 1950s and 60s, Cowie et al. (1980) in the UK and Lyons (1958) in the U.S. used their considerable surgical skills to advance the understanding of the endocrine control of lactation in both ruminants and laboratory mammals. The removal of the pituitary gland from marsupials, rats, mice, sheep, goats and rabbits abruptly terminates lactation (Forsyth 1983). Furthermore, in most species, adrenalectomy but not ovariecotomy also causes a rapid decline in milk production. The minimum combination of hormones required to restore milk production varies among species; the rabbit requires only prolactin, whereas goats require adrenal corticoid, triiodothyronine, growth hormone and prolactin. In nonruminants (pigs, dogs, rats or women), milk production decreases rapidly if prolactin secretion is inhibited, but in ruminants (goats, cows or sheep), growth hormone seems to replace prolactin in importance for the maintenance of lactation. Furthermore, metabolic hormones such as prolactin, growth hormone, insulin and triiodothyronine may have both local effects on the mammary tissue and systemic effects on metabolism in other tissues and on nutrient partitioning.

**Local.** Linzell and Peaker (1971) first hypothesized that milk production could be modulated by hormone(s) in milk. They found that hourly, unilateral milking of one mammary gland of the goat increased the rate of synthesis of milk in that gland and proposed that milk synthesis was regulated by the build-up of inhibitory compound(s) within the alveolus. Furthermore, they proposed that the removal of milk from the gland removed these inhibitory compound(s) and promoted increased milk synthesis.

The nature of the local control on milk synthesis is complex and multifactorial. There is evidence that there are at least two mechanisms operating within the mammary gland of ruminants and laboratory animals. One mechanism regulates the synthesis of milk fat (Heesom et al. 1992) and the other involves a small protein (feedback inhibitor of lactation (FIL)), which modulates the synthesis of lactose and milk protein by inhibiting the formation of secretory vesicles in the Golgi apparatus (Wilde et al. 1995).

There is also strong support for the local control of milk synthesis in women. We have used a computerized breast measurement system (Cox et al. 1997) to measure the short-term rates of milk synthesis in women by determining the rate of increase in breast volume between breast-feedings. Daly et al. (1993) and Cox et al. (1996) found that the degree of fullness of the breast and the short-term rate of milk synthesis were inversely related and that, during the day, within women, right and left breasts showed wide but inconsistent (the highest rates of milk synthesis were not always observed in one particular breast) variation in the short-term rates of milk synthesis. These observations and the fact that the inhibitory protein (FIL) has been found in human milk (Prentice et al. 1989) are consistent with the autocrine control of human milk synthesis (Wilde et al. 1995).

Thus the maintenance of milk production in all mammals appears to be under three levels of control (endocrine, autocrine and metabolic). In lactating women in developed countries, who breast-feed on demand, it is likely that local autocrine and metabolic factors are more important than endocrine mechanisms. Wilde and Peaker (1990) argue that genetically controlled parental investment analysis (cost to the mother vs. benefit to the offspring) occurs at parturition and that this “investment analysis” incorporates maternal nutritional status and is mediated to the mammary glands by the endocrine system. Although this strategic appraisal is believed to set the maximum rate of milk secretion (Peaker 1989), the response is modulated by autocrine control mechanisms operating within each mammary gland. Hence it is the local control mechanisms that respond to milk removal to ensure that supply equals infant demand.

In support of this, Cox et al. (1996) could not find any relationship between basal or suckling-stimulated blood prolactin and either the short- or long-term rates of milk synthesis. Thus it is probable that in these women the endocrine system has set each individual woman’s maximum potential to produce milk, but the infant’s appetite is regulating the short-term and daily milk production within each breast such that milk synthesis matches infant demand. Furthermore, because the short-term (between breast-feedings) rate of milk synthesis can vary more than fivefold during the day, the demand for substrates for milk synthesis would also vary greatly during the day. A variable demand over the day for glucose for milk synthesis could have important implications for glycemic control in insulin-dependent diabetic women.

Women in traditional societies have been observed to have a much greater frequency of breast-feeding, several times each hour rather than several times each day (Hartmann et al. 1984, Konner and Worthman 1980). Thus it is possible that the breasts of these women never accumulate enough milk between breast-feedings to invoke autocrine control processes. Under these circumstances, metabolic and endocrine mechanisms rather than the infant’s appetite may limit milk synthesis.

ENERGY OUTPUT IN MILK

Currently, the most reliable estimates of the energy content of human milk have been derived from milk samples obtained over a 24-h period by expression of either alternate breasts for each breast-feeding or of one breast three times daily. The mean values for 1–6 mo of lactation range from 2.22 ± 0.29 to 2.96 ± 0.38 kJ/g (Neville 1995), giving an unweighted mean of 2.66 kJ/g. Neville also reviewed the milk intake of an exclusively breast-fed infant and concluded that the average was about 770 g/d with a wide range (from 500 to 1200 g/d). Therefore, on the basis of the above values, the daily output of energy in the milk of a woman exclusively breast-feeding a single infant could range from as low as 1.11 MJ/d to as high as 3.55 MJ/d with a mean of 2.05 MJ/d. Although it is unlikely
that the infants with milk intakes at the lower end of the range are receiving milk of the lowest energy density, it is of interest that this range is consistent with our results, which showed a coefficient of variation of 25% for the energy content of 24-h milk productions in Perth women (Hartmann et al. 1995).

Furthermore, the differences that we have recently found for 24-h measurements of fat in milk from individual breasts (Fig. 1) support this wide variability. In view of the current interest in the Barker hypothesis [that long term adult health is related to fetal and neo-postnatal growth and health (Barker 1992)] and the wide range of energy intakes shown for exclusively breast-fed infants, the relationship between energy intake, growth rate and health in both the short and long term requires further investigation.

**EFFICIENCY OF MILK SYNTHESIS**

In the last 25 years, estimates of the efficiency of converting maternal energy into milk energy in women have varied from 79 to 90%. Although earlier investigators used either measured or estimated energy balance values to calculate efficiency, Prentice and Prentice (1988) and Prentice et al. (1996) calculated the overall food-to-milk-energy conversion efficiency associated with the synthesis of milk macronutrients. This calculation included both the biochemical efficiency of the synthesis of these macronutrients and the costs of digestion, absorption, interconversion, transport and storage of dietary carbohydrate, fat and protein. Given the limitations of this approach and the data available for calorimetric efficiencies of milk production in a number of species, they calculated that the efficiency for the dietary-to-milk-energy conversion in women was unlikely to exceed 80%. Furthermore, milk synthesis would be expected to be more efficient in women who use their own body fat and lose weight during lactation than in those who do not and in women consuming high fat rather than low fat diets (Warwick 1989).

From the energy content of milk and the efficiency of milk synthesis, it can be calculated that for a woman exclusively breast-feeding her baby at 3 mo of lactation, milk production would require on average 2.56 MJ/d but could range from 1.38 to 4.43 MJ/d for individual women, depending on the production and energy density of their milk. The significance of the amount of energy required for milk production can be evaluated when compared with recommended dietary intakes for nonpregnant, nonlactating women. Milk production represents ~25% on average of the recommended intake for women exclusively breast-feeding single infants and as much as 50% of the recommended energy intake for those breastfeeding twins (Saint et al. 1986).

Therefore, milk production presents a challenge to the mechanisms that control metabolic homeostasis. The increased energy requirement for milk production can be met by either one or a combination of the following: increasing dietary energy intake, decreasing physical activity, increasing the efficiency of metabolism [decreasing basal metabolic rate (BMR)], reducing postprandial metabolism or mobilizing tissue energy reserves (Brown and Dewey 1992). Different mammals adopt different strategies; for example, body reserves are of paramount importance to baleen whales. Female blue whales feeding in the Antarctic increase their body weight by 50% before migrating to warmer waters to calve. This stored mass is lost during 7 mo of lactation during which the fasting mother puts about 17,000 kg onto her calf (Oftedal 1993). The first few months of lactation do not impose significant metabolic demands upon the kangaroo, whereas in a rat with 6–8 pups, food consumption increases three- to fourfold, and the gastrointestinal tract undergoes major hypertrophy to deal with the extra nutrient load (Lunn 1994).

**ENERGETIC STRESS AND LACTATION IN WOMEN**

Apart from the metabolic differences between species (ruminant vs. nonruminant), there are other important physiologic differences between lactation in dairy cows and women. In the dairy cow, milk production is much greater than what is required for the survival of her calf, all available milk is removed at each milking, milk synthesis from hour to hour is relatively constant over the long intervals between milkings, other energy-demanding stresses are minimized, and the quantity and quality of the diet is regulated in accordance with milk production. By contrast, in women, the infant’s appetite determines the amount of milk removed at a breast-feeding, the short-term rate of milk synthesis can vary greatly, physical exercise is not necessarily minimized and dietary intake can vary greatly. Therefore, unlike in dairy animals, the partitioning of nutrients for lactation in women cannot be generalized to all lactating women but must be related to individual women, taking into account their particular metabolic circumstances.

**Endocrinology.** Lactation in women is characterized by a series of endocrine events. The falling levels of progesterone after parturition accompanied by the enhanced effects of prolactin, oxytocin and the adrenal corticoids are the hormonal triggers required to initiate lactogenesis stage II, the onset of copious milk supply (Cowie et al. 1980). In addition to these changes, there is also a disruption in the pulsatile release of gonadotrophin-releasing hormone from the hypothalamus, which in turn results in decreased secretion of lutetizing hormone from the pituitary, resulting (when coupled with low or even normal follicle-stimulating hormone levels) in lactational amenorrhea in women (McNeill et al. 1994).

Lactation has also been shown to be related to decreases in endocrine responses to stress. The reduced corticosterone response to stress in lactating rats was reported by Thomann and colleagues in 1968 and confirmed by Schlein et al. in 1974. Further research in rats revealed that lactation buffered the responses of prolactin, catecholamines (Higuchi et al. 1989) and oxytocin to stress as well as normal hypothalamic stress responses (Lightman and Young 1989). Recent research has found that these characteristics are conserved in lactating women. Altemus and co-workers (1995) found that plasma adrenocorticotrophin, cortisol and glucose responses were all significantly attenuated in lactating women. Furthermore, basal norepinephrine levels were also reduced. These changes in maternal endocrinology may represent homeorhetic adaptations required to support the dominant physiologic state of lactation. The blunting of typical stress responses [increased fat mobilization, increased glycogen conversion to glucose, increased liver gluconeogenesis and alterations to the reticul activating system of the brain (Solomon et al. 1996)] helps to conserve energy required for lactation (Altemus et al. 1995, Higuchi et al. 1989) and protect the mother against the stress-related inhibition of lactation (Altemus et al. 1995).

**Diet.** It is estimated that an extra 2.1 MJ/d is needed to provide the energy required for human lactation (WHO 1985). Lunn (1994) reviewed the energy requirements during lactation and concluded that, in developed countries, for the first 3 mo of lactation, almost two thirds of the increased energy requirements for lactation were met by increased food intake and one third by decreased physical activity. The mobilization
of body reserves has also been implicated in providing energy to sustain lactation. Goldberg and co-workers (1991) found no net changes in body weight or fat content in the first 3 mo of lactation as did Sadurskis et al. (1988) and van Raaij et al. (1990) for the first 2 mo of lactation. These results would seem to indicate that body reserves laid down in pregnancy are not mobilized during early lactation. However, both van Raaij et al. and Sadurskis et al. showed that for women breast-feeding 2–6 mo postpartum, the average weight and fat mass losses amounted to 70–120 kcal/d. In a recent review, Dewey (1997) concluded that lactating women in affluent populations lose, on average about 500 g/mo (155 kcal/d), although the duration of lactation required to achieve this loss is not stated. Clearly, with such a large variation of results, it is difficult to assume that all women will be able to subsidize lactation through the mobilization of their own fat stores (Dewey 1997). However, it does seem that to maximize the mobilization of fat stores mothers have to breast-feed for 6 mo or more.

Lunn (1994) found that in women in The Gambia, lactation was not related to decreased physical activity, and reductions in BMR and diet-induced thermogenesis were negligible weight rather than the presumed energy requirements for milk production. It does seem that to maximize the mobilization of fat stores the demands for milk synthesis in women suggests that recommendations for the partitioning of nutrients among well-nourished individuals are still as poorly understood in women as in dairy cows (Bell 1995). Nevertheless, the flexibility in both homeostatic and homeorhetic adaptations to the energy demands for milk synthesis in women suggests that recommendations for dietary energy intake during lactation should address current weight status and would serve women better if they were based on the desired postweaning outcome for body weight rather than the presumed energy requirements for milk production (Hartmann et al. 1995).

### LITERATURE CITED


Konner, M. & Worthman, C. (1993) Frequencies of dietary intakes in third and fourth trimesters of pregnancy and the first month postpartum (Lawrence and Whitehead 1988), other studies (Panter-Brick 1993) in developing countries have found that lactating women do not appear to conserve energy by changing patterns of physical activity. Thus reduced physical activity is also important to ensure that highly trained, exercising lactating mothers have to breast-feed for 6 mo or more.

Exercice. In Western women with sedentary lifestyles, savings on physical activity during lactation are very limited. van Raaij et al. (1990) reported that the net cost of physical activity in their Dutch subjects was 210 kJ/d lower during the first 6 mo of lactation than at 1 y postpartum. Although, there are reports of a reduction in the work output of women in The Gambia in the third trimester of pregnancy and the first month postpartum (Lawrence and Whitehead 1988), other studies (Panter-Brick 1993) in developing countries have found that lactating women do not appear to conserve energy by changing patterns of physical activity. Thus reduced physical activity is not always an option for economizing on energy requirements during lactation.

Dewey’s group studied the influence of exercise on lactation in women in the U.S. A high level of physical activity in either highly trained, exercising women or in women randomly selected to take part in an exercise program did not compro-

mise milk production because the energy expended in exercise was compensated for by an increase in dietary energy intake (Dewey and McCrory 1994). However, attention should be given to nitrogen balance in exercising lactating women. In dairy cows, the extra demand for amino acids for milk production is met in part by mobilization of “labile protein reserves” from liver and skeletal muscle (Bell 1995). Therefore, it may be important to ensure that highly trained, exercising lactating women are not in negative nitrogen balance.

Although the overall metabolic pathway for energy production was described by Lavoisier more than 200 years ago, the mechanisms involved in both homeostatic and homeorhetic regulation for the partitioning of nutrients among well-nourished individuals are still as poorly understood in women as in dairy cows (Bell 1995). Nevertheless, the flexibility in both homeostatic and homeorhetic adaptations to the energy demands for milk synthesis in women suggests that recommendations for dietary energy intake during lactation should address current weight status and would serve women better if they were based on the desired postweaning outcome for body weight rather than the presumed energy requirements for milk production (Hartmann et al. 1995).
HOMEOSTATIC REGULATION OF LACTATION

399S


