LACTATION | Galactopoiesis, Effects of Hormones and Growth Factors

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0001 # LACTATION

Galactopoiesis/Effects of Hormones and Growth Factors

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Introduction

0002 The term 'galactopoiesis' was originally coined to describe the enhancement of an established lactation. In this sense, only exogenous somatotropin (ST) and thyroid hormone are clearly demonstrated galactopoietic agents in dairy animals, suggesting that these hormones are endogenously rate-limiting. However, in a more inclusive sense, galactopoiesis has been used to describe the maintenance of lactation. A number of hormones and factors are involved in the maintenance of milk production in dairy animals and these will be described in this review.

0003 Galactopoietic hormones, growth factors and regular milk removal are essential for regulation and maintenance of lactation. The pituitary gland and its hormones are essential integrators of the endocrine regulation of milk secretion. Milk production of goats declines precipitously after hypophysectomy, but yield can be fully restored to prehypophysectomy levels by the combined administration of prolactin (PRL), ST, glucocorticoids and triiodothyronine (T_3) (**Figure 1**). Although there clearly are species differences, endocrine organ ablation/replacement studies have shown that PRL, ST, glucocorticoids and thyroid hormones are typically required for the full maintenance of lactation. Still, additional hormones and growth factors (both humoral and local, identified and unidentified) are probably important for the normal physiological maintenance of lactation. In addition to regulatory factors that actively support synthesis of milk components, frequent emptying of the mammary gland is critical. This process is supported by the milking-induced release of oxytocin. Physiological support for both processes – milk synthesis and milk removal – is necessary for maintenance of lactation. Other factors that can affect the maintenance of lactation are those that impinge upon the maintenance of the secretory cell population by decreasing cell loss or by increasing cell proliferation. These factors do not impact the secretory capacity of existing cells but impact the secretory capacity of the mammary gland as well as the shape and length of the lactation curve.

Somatotropin

0004 The ability of a crude extract of anterior pituitary to increase milk production in goats and cows was first demonstrated in the 1930s. Identification of ST or growth hormone as the active component occurred in the 1940s. Since then, there has been much progress in understanding the galactopoietic activity of ST in dairy animals, although questions regarding its mode of action remain. Progress was greatly accelerated in the last decade by the advances in molecular biology that allowed production of commercial quantities of bovine ST (bST).

0005 The clearest galactopoietic activity of ST appears to be in co-ordinating changes in tissue metabolism that promote a flux of nutrients and energy to the mammary gland. Two tissues that play prominent roles in this process are adipose and liver tissues. These actions appear to be largely mediated by ST receptors in these tissues. In adipose tissue, ST inhibits lipogenesis when animals are in positive energy balance and promotes lipolysis when animals are in negative energy balance. In liver, ST promotes gluconeogenesis, which is particularly important in ruminants in which nutrient absorption provides a negligible percentage of the glucose required for milk synthesis. In other tissues, the galactopoietic activity of ST appears to be mediated by other members of the somatotropin axis including the insulin-like growth factors (IGF), most prominently IGF-I and insulin-like growth factor binding proteins. In muscle and other body tissues, ST decreases glucose utilization and oxidation of amino acids. The net

result of these metabolic changes is to conserve nutrients and energy for synthesis of milk lactose, protein and lipid. A direct action of ST has not been observed in lactating mammary tissue, and functional ligand binding assays have failed to detect receptor protein. The IGFs and their binding proteins appear the most likely mediators of effects on the lactating mammary gland whereby ST increases milk synthesis.

0006 For a more complete discussion of the galactopoietic activity of ST and insulin-like growth factors see **Lactation:** Galactopoiesis/Effects of bST Treatment (0235).

Thyroid Hormones

0007 Involvement of the thyroid in maintenance of lactation has long been appreciated. In 1918, Grimmer reported that milk yield was reduced in thyroidectomized goats. Subsequently, in 1934, Graham showed that thyroidectomy of dairy cows reduced milk yield; conversely, treatment with the thyroid hormone thyroxine increased milk yield by approximately 20%. Because thyroxine is efficacious when fed, these results aroused considerable interest in the practical utilization of the hormone to increase milk production in cattle. This was made economically feasible by the manufacture of thyroxine and thyroactive iodinated proteins at reduced cost. However, results of numerous experiments indicated that while feeding thyroxine (or iodinated protein) increased milk production by 10–40%, the galactopoietic effect was of variable duration and milk production returned to normal or below normal levels despite continued treatment. The galactopoietic effect of thyroxine supplementation appears to be due to a general increase in body metabolism. Thus, thyroxine supplementation is not effective when cows are in early lactation (negative energy balance) and are mobilizing body reserves to meet the energy demands of lactation. A general increase in body metabolism at this time would be contrary to meeting the nutrient demands of lactation. It was concluded that thyroxine treatment should not be initiated before midlactation and that energy density of the diet should be increased during treatment because feed intake does not increase in proportion to increased energy utilization. Furthermore, upon withdrawal of treatment, a hypothyroid condition ensues that exacerbates the decline in milk yield. Despite an initial interest in thyroid hormone supplementation to increase milk yield, the temporary nature of the milk yield response and frequent overshoot below normal production led to the conclusion that its adoption would be of minimal value.

0008 In addition to a general effect on metabolic rate, thyroid hormones potentiate the activity of other lactogenic and galactopoietic hormones. Triiodothyronine enhances the ability of PRL to stimulate lactose synthetase in mouse mammary tissue cultures approximately fivefold, and enhances PRL stimulation of casein synthesis in rabbit mammary tissue culture. Similarly, for oestradiol to stimulate lactogenesis in mouse or bovine mammary tissue culture, T_3 must be present in the culture medium.

0009 In contrast to the general increase in metabolism evident with thyroid hormone supplementation, organ-specific changes in thyroid hormone metabolism occur during lactogenesis that may facilitate adaptation to a lactational state by promoting differential rates of energy utilization. Although thyroxine (T_4) is the predominant thyroid hormone in the circulation, it may be viewed as a prohormone because it has little, if any, biological activity. The most metabolically active thyroid hormone, 3,3′,5-triiodothyronine (T_3), is produced by enzymatic 5′deiodination of T_4 within the thyroid and peripheral tissues. The extrathyroidal activity of thyroxine-5′-deiodinase (5′D) is an important regulator of localized T_3 availability in animal tissues during various physiological states. With onset of lactation in rodents and ruminants, there is an increase in 5′D in mammary gland and a decrease in liver. These changes should maintain a euthyroid state in the mammary gland while promoting a hypothyroid condition for the body as a whole. The transfer of iodine, iodinated nonhormonal compounds and thyroid hormones through the mammary gland into milk further promotes a systemic hypothyroid condition. Maintenance of a euthyroid state in the lactating mammary gland in the midst of a functional hypothyroid condition is consistent with increasing the metabolic priority of the mammary gland and providing T_3 to potentiate the effect of other galactopoietic hormones.

0010 The opposite organ-specific changes in thyroid hormone metabolism are proportional to lactational intensity in rodents and appear to be involved in eliciting a response to galactopoietic hormones. In mice, thyroid hormones are necessary to obtain milk production increases in response to ST and PRL, and it has been demonstrated that mammary 5′D is uniquely responsive to galactopoietic hormones. Both ST and PRL increase 5′D activity in murine mammary gland, but do not alter activity in liver or kidney. Similarly, changes in 5′D activity are hypothesized to mediate or augment the galactopoietic effect of bST in dairy cows. However, results are not as consistent as those in rodents, and further investigation is necessary to clarify the interaction

between thyroid hormone metabolism and bST-increased milk production in cattle.

0011 The relationship between ST and thyroid hormones is not limited to ST-induced alterations in 5′D during lactation and galactopoiesis. There is a close relationship between thyroid hormones, thyroid hormone metabolism, ST and IGF-I synthesis. Mechanistically, T_3 can alter hepatic ST receptor binding and thus enhance ST stimulation of IGF-I synthesis, or T_3 can increase IGF-I synthesis in the absence of ST. It is worth noting that in those situations in which ST does not stimulate IGF synthesis (e.g. during food restriction, foetal development, sex-linked dwarfism and hypothyroidism) there is evidence for T_3 deficiency. In addition, T_3 serves as a regulator of ST synthesis by the pituitary. Conversely, ST can alter synthesis of 5′D and the peripheral production of T_3.

Prolactin

0012 The pituitary hormone prolactin (PRL) was named in deference to its pro-lactational effects. However, species differ with regard to their sensitivity to PRL and its impact on lactation. In rodents and primates, PRL is mammogenic (particularly during pregnancy), is lactogenic and is the primary galactopoietic hormone. However, in ruminants, PRL plays a less dominant role in mammary gland physiology. In these dairy animals, PRL is a primary lactogenic hormone, but its galactopoietic activity is subtle and its mammogenic activity is questionable. In ruminants, ST is thought to be the primary galactopoietic hormone and PRL a minor player. The opposite appears to be the case in other species.

0013 It is clear that the mammary epithelium responds directly to PRL. Receptors for the hormone have been identified in mammary epithelial cells of numerous species, and these receptors have been characterized as members of the cytokine receptor superfamily. The receptors do not have intrinsic kinase activity, but associate with the Janus kinase (JAK) family of tyrosine kinases that, when activated by receptor binding and dimerization, phosphorylates cellular proteins. Of primary importance appears to be phosphorylation of the signal transducer and activator of transcription-5a (Stat5a). Stat5a is a key regulator of casein transcription in keeping with a role for PRL in lactogenesis and galactopoiesis.

0014 In contrast to laboratory rodents, a galactopoietic role for PRL in dairy animals is not easily demonstrable. In lactating mice, rats and rabbits, administration of ergot alkaloids (inhibitors of pituitary PRL secretion) to decrease circulating concentration of PRL markedly reduces milk production (50–100%). Conversely, administration of PRL to mice and rats increases milk yield. In lactating ruminants, treatment with ergot alkaloids has little effect. There is no effect in lactating dairy cows, and a small (~10%) reduction of milk yield in lactating goats and sheep. (In contrast, preventing the preparturient increase in plasma PRL concentrations markedly reduces milk production during early lactation, demonstrating the importance of PRL for the final stage of lactogenesis.) Additionally, when PRL treatment of lactating hypophysectomized goats is terminated without eliminating treatment with ST, glucocorticoid and T_3, there is no apparent decline in milk production (**Figure 1**). Conversely, when dairy cows were treated with PRL for a 14-day period before peak lactation and again after peak lactation, milk production was not affected, nor was milk composition affected except for a 10% increase in α-lactalbumin concentration in milk of cows treated during early lactation. However, PRL has occasionally increased milk yield in lactating dairy goats. Thus, data suggest that availability of PRL is not rate-limiting to lactation of dairy cows, but small increases in milk production may be realized by PRL treatment of dairy goats.

0015 The conclusion that increasing plasma PRL does not increase milk production of dairy cows has been difficult to accept. There is a small correlation of milk production and plasma PRL in dairy cows, but a strong correlation between the milking-induced release of PRL and milk production. As lactation progresses, milk production and the release of PRL at milking both decline. It is not known whether this relationship is physiologically relevant. Additionally, increased photoperiod significantly increases milk production while increasing plasma PRL. Recently, it has been shown that increased photoperiod also increases plasma IGF-I (without increasing ST) and this has been hypothesized to mediate the milk production effect of photoperiod. Still, the ability of IGF-I to induce an increase in milk production is not certain, and subtle effects of PRL on milk production, particularly long-term effects, are possible.

0016 Regardless of the ability or lack of ability of PRL to increase milk production in a relatively short timeframe, recent data suggest that it may help to maintain the population of mammary secretory cells and thus promote lactational persistency (**Figure 2**). This was first proposed by Flint and Gardner who discovered that treatment of lactating rats with ergot alkaloids decreased milk production approximately 50%, compromised epithelial tight junction integrity and reduced DNA content of the mammary gland by 20–25%. When PRL concentrations were reduced significantly, increased epithelial cell apoptosis occurred, with an accompanying disruption of the

blood–milk barrier and decline in number of secretory cells. Maintenance of the mammary epithelial cell population appears to involve an interaction between the PRL and ST axes. However, this requires further investigation in ruminants.

Insulin-Like Growth Factors

0017 Insulin-like growth factors appear to be essential participants in the galactopoietic response to exogenous bST. When the production of IGF-1 is uncoupled from ST regulation, such as occurs during negative energy balance, then a milk production response to bST is abrogated. Infusion of IGF-I into the close arterial supply to the mammary gland of goats rapidly increased milk synthesis. These data strongly support a galactopoietic role for IGF-I. Galactopoietic activity of IGF-II is uncertain.

0018 Additionally, IGF-I is a mammary mitogen and survival factor. The ability of IGF-I to induce cell proliferation has been demonstrated in numerous *in vitro* and *in vivo* mammary model systems. Recently, administration of bST was shown to increase the percentage of mammary epithelial cells expressing Ki-67, a nuclear antigen marker for cell proliferation, approximately threefold. It is proposed that this apparent proliferation response to bST is mediated by IGF-I. Such increased cell renewal would limit the decline in number of mammary epithelial cells that occurs with advancing lactation and accounts for the steady decline in milk production after peak lactation. Regulation of mammary apoptosis in rats seemingly involves an interaction between PRL and IGF-I. Reduction of plasma PRL by ergot alkaloids decreases milk secretion, accompanied by an increase in the incidence of apoptosis in the mammary gland. Prolactin appears to depress the synthesis of IGF-binding protein-5 (IGFBP-5), thus limiting its ability to bind IGF-I and suppress its cell survival activity. Thus, PRL is thought to promote cell survival so that the outcome of PRL insufficiency is increased mammary apoptosis. Whether IGFBP-5 or an analogous IGFBP is regulated by PRL in the mammary glands of ruminants remains to be demonstrated. However, in ruminants, bST increases lactational persistency and maintains mammary cell number as lactation advances by increasing cell renewal or increasing cell survival.

Insulin

0019 Insulin is clearly a hormone that plays an important role in the regulation of nutrient utilization during lactation. In ruminant dairy animals, insulin has no effect on the mammary uptake of glucose, acetate, β-hydroxybutyrate and amino acids, but exogenous insulin inhibits milk production by virtue of its metabolic effects on other tissues. For example, in adipose tissue, insulin promotes the uptake of glucose and acetate and stimulates lipogenesis while inhibiting lipolysis, while in liver it inhibits gluconeogenesis. However, the homeorhetic attributes of bST are largely realized by virtue of its ability to inhibit selected processes that are stimulated by insulin (see **Lactation:** Galactopoiesis/Effects of bST Treatment (0235)). It is unlikely that insulin plays a role in regulating the number of mammary epithelial cells. Mammogenic properties that were historically attributed to insulin on the basis of its effects on mammary cells *in vitro* can be dismissed as artifactual. Due to the use of supraphysiological concentrations of insulin in these systems, the mitogenic activity observed is attributed to the ability of insulin at high concentration to cross-react with IGF receptors and elicit IGF-related responses.

Glucocorticoids

0020 In rats and mice, it has been known that adrenalectomy severely reduces milk yield, and conversely that administration of glucocorticoids to intact animals increases milk yield by retarding the decline that occurs with advancing lactation. Because the decline in milk yield during a murine lactation is due to decreased activity of mammary secretory cells, rather than a decrease in cell number, it follows that the galactopoietic effect of glucocorticoids in rodents occurs because they are rate-limiting to milk synthesis. It was determined that glucocorticoids bind to specific glucocorticoid receptors in mammary tissue and regulate the secretion of α-lactalbumin and β-casein. Some of these actions are synergistic with other regulatory hormones such as PRL. For ruminants, there is little evidence that the glucocorticoids are limiting to milk production. However, adrenalectomy reduces milk yield that is restored by glucocorticoid treatment. Bovine mammary tissue contains glucocorticoid receptors that are present in greater concentration in lactating than in prepartum tissues, and receptor number correlates with glucose uptake. Certainly, glucocorticoids are important for maintenance of milk production in dairy species.

Hormones of Pregnancy

0021 Unlike most species, dairy cows are typically pregnant through the greater part of lactation, and goats may be in late lactation when pregnant. Conse-

quently, hormones of pregnancy can impact lactation. One of these hormones is produced by the placenta (binucleate cells of the trophoblast), is a member of the somatotropin–prolactin family and is known as placental lactogen. The relative lactogenic and somatotropic activities of placental lactogen vary with species. In ruminants, placental lactogen has greater homology with PRL than ST, although it binds to both lactogenic and somatogenic receptors. Concentrations of placental lactogen in the maternal circulation of dairy cows are very low, whereas concentrations in the maternal blood of sheep and goats are quite high (100–1000-fold greater than for cows). Concentrations peak during the last trimester of pregnancy. Exogenous placental lactogen stimulates milk production by mechanisms that differ from those that mediate the galactopoietic effects of ST. Compared with bST treatment, placental lactogen treatment of dairy cows or ewes increases milk production more slowly and does so without increasing lipolysis. Unlike in bST treatment, feed intake for placental lactogen-treated cows increased rapidly. Its biological function appears related to maternal partitioning of nutrients. Under usual circumstances, the physiological impact of placental lactogen on the mammary gland is likely on mammary growth and lactogenesis in animals that are not lactating when pregnant, and on growth and lactogenesis during the periparturient dry period in animals that are lactating during pregnancy.

0022 In contrast to potential galactopoietic effects of placental lactogen, concomitant pregnancy decreases the persistency of lactation, with an accelerated decline in milk production occurring during the last months of pregnancy. The reasons for this decline are unclear, but certainly physiological processes that promote foetal growth and vigour take precedence over milk production. Other hormones of pregnancy that probably impact mammary gland function are oestrogen and progesterone. High concentrations of oestrogens decrease milk yield, while progesterone does not. Although progesterone inhibits lactogenesis partly because of its ability to competitively inhibit binding of glucocorticoid to the glucocorticoid receptor, the inability of exogenous progesterone to impact lactation in many species is due to the lack of progesterone receptors during lactation. In dairy cows, this inability is due to a reduction in number of progesterone receptors rather than an absolute absence of the receptors in the lactating gland. The mechanism by which estrogens decrease milk production is unclear.

Milk Removal

0023 Removal of milk from the mammary gland is a necessary component for maintaining lactation. This is evident from the decreased persistency of lactation with incomplete milking and conversely from the enhanced lactation persistency in response to the facilitation of milk removal by daily injections of oxytocin at milking.

0024 In the absence of milk removal, intramammary pressure increases, blood flow to mammary tissue decreases, and a substance(s) that inhibits milk secretion and promotes apoptosis apparently accumulates within the alveolar milk. In the short term, such as prolonged milking interval, lack of milk removal causes partial inhibition of milk synthesis and secretion; in the long term, it causes the termination of lactation and initiation of mammary involution. Considerable research effort has been expended in attempts to identify products in milk that feed back to inhibit milk secretion. Initial research tentatively identified a substance with appropriate characteristics that was referred to as feedback inhibitor of lactation (FIL), but the substance has not been purified and identified or its gene identified. Currently, a naturally produced proteolytic fragment of casein has been identified, and the synthesized peptide sequence has been shown to inhibit milk synthesis. These latter results are preliminary but intriguing. Additionally, milk accumulation produces leakiness of the tight junction complexes between epithelial cells. Artificially increasing tight junction leakiness decreases milk secretion by mechanisms as yet undetermined, but may well involve signal transduction through the cytoskeleton.

0025 The benefits of frequent milking are multifaceted. Increasing milking frequency from twice daily to thrice daily increases milk production by approximately 20%. This increase accrues largely because of the removal of the inhibitory effects of milk accumulation. In the short term, increased milking frequency appears to cause increased cellular activity, whereas in the long term, glands milked more frequently have a greater number of cells. Because these results can be demonstrated by milking glands within the same udder at different frequency, the effects are presumably due to local effects rather than systemic. Limited studies indicate that the rate of decline of milk production after peak lactation (persistency) is the same in thrice-daily and twice-daily milked cows. Finally, increased milk production can be realized by temporarily utilizing increased milking frequency during early lactation. This carryover effect suggests that the increased milking frequency induces an increase in mammary cell number and thus an effect

that persists through the lactation. Conversely, it was demonstrated over 30 years ago that a temporary reduction in milking frequency during early lactation causes a decrease in milk yield that persists for that lactation. Although the effect of milking frequency appears to be largely mediated by local effects, one should not rule out an interaction with the galactopoietic hormones that are released at each milking in addition to oxytocin. These hormones include PRL and glucocorticoids, as well as ST in goats and rats, but not in cows or humans.

Other Mitogens and Survival Factors

0026 As mentioned previously, increased expression of mitogenic factors and cell survival factors in the mammary gland can increase milk production by virtue of effects on the size and maintenance of the secretory cell population (**Figure 2**). Beyond the classical hormones and growth factors already discussed, there are many factors that can impact cell turnover. A number of reviews concerning mammary growth factors have been published and it is beyond the scope of this review to consider the variety of factors that have been investigated. A greater understanding of known factors, and the potential discovery of new factors will increase our understanding of processes that can regulate persistency of lactation and provide the tools to do so.

See also: **Lactation:** Lactogenesis (0231); Galactopoiesis/Lactation Curves (0232); Galactopoiesis/Effects of bST Treatment (0235). **Mammals** (0743).

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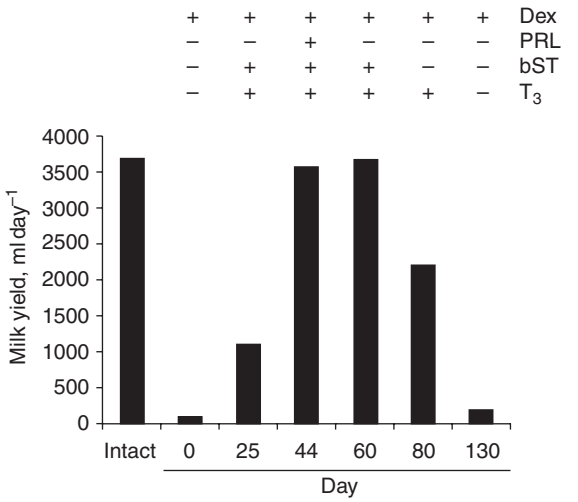
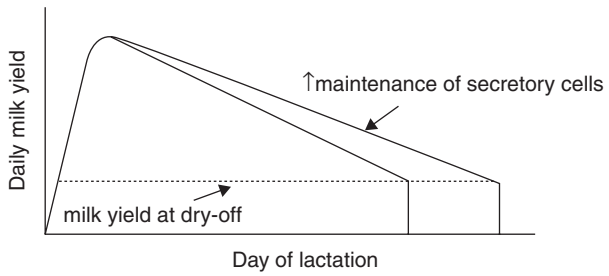


F0001 **Figure 1** Daily milk yields of a goat after hypophysectomy and during replacement hormone therapy. The goat was producing approximately 3700 ml of milk per day prior to hypophysectomy (Intact). After treatment with dexamethasone for 2 months, milk production was as shown at time 0 in the figure. Milk production is depicted after addition or removal of the hormones as depicted. PRL = prolactin, bST = somatotropin, T_3 = triiodothyronine, Dex = dexamethasone. (Adapted from Cowie, A T (1969) *Lactogenesis: The Initiation of Milk Secretion at Parturition*. University Press.)



F0002 **Figure 2** Effect of maintenance of the secretory cell population on the lactation curve. Increased maintenance of the secretory cell population increases the persistency of lactation as evident by a decrease in the slope of the declining phase of milk production. Length of lactation is increased if milking is terminated at a similar daily production.