

Implications of a Dysfunctional Somatotrophic Axis During the Transition Period in Dairy Cattle

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Summary:

- During the transition period, dairy cattle experience physiological and metabolic changes that can affect subsequent cow health, productivity and reproductive competence.
- Metabolic adaptations during the transition period are coordinated by homeorhetic regulators such as growth hormone.
- During the transition period:
 - Dry matter intake decreases
 - Energy balance is in a negative state
 - Non-esterified fatty acid concentrations increase
 - Plasma growth hormone (GH) concentrations are elevated
 - Plasma insulin-like growth factor (IGF) I concentrations are low.
- Poor galactopoietic and plasma IGF-I responses to exogenous GH during the transition period may be due to decreased hepatic GH receptor abundance.
- The GH/IGF-I system may be involved in the metabolic regulation of reproductive performance.
- Members of the GH/IGF-I system are expressed throughout the bovine reproductive tract, and changes in expression may affect fertility.

Introduction

In high yielding dairy cows, the onset of lactation increases the total energy requirements by approximately four-fold, reflecting mostly the needs of the mammary gland for milk synthesis precursors such as glucose and amino acids (Bell, 1995; Drackley et al., 2001). Because the hyperphagia required to meet those demands develops slowly, shortfalls are met by mobilization of endogenous reserves and by shifting the pattern of nutrients used by non-mammary tissues (Bauman and Currie, 1980; Bell, 1995).

Defects in the timing or amplitude of metabolic adaptations increase susceptibility of transition dairy cows to disorders such as ketosis and hepatic lipidosis (Goff and Horst, 1997; Ingvarsen et al., 2003). Periparturient diseases have immediate and long-term negative effects on milk production and on other determinants of profitability such as reproduction (Drackley, 1999; Butler, 2000). These observations have prompted intensive efforts to characterize metabolic events underlying a successful transition period, and to identify defects leading to diseased states and impaired reproductive performance.

Metabolic adaptations during the transition period are coordinated by changes in the concentrations and actions of homeorhetic hormones (Bauman and Currie, 1980). Experimental evidence of homeorhetic action is particularly strong for growth hormone (GH; Bauman, 2000). Paradoxically, some of the actions of GH are significantly attenuated or lost during the transition period, particularly in early lactation. In this review, we will examine the molecular basis for impaired GH-dependent processes during the transition period and subsequent effects on the reproductive performance of dairy cattle.

Metabolic Adaptations During the Transition Period

The transition period in dairy cattle is defined as three weeks before parturition to three weeks after parturition (Ingvartsen and Andersen, 2000). During the transition period the nutrient requirements of the high-yielding dairy cow increase substantially to meet the demands of conceptus growth during late pregnancy and the onset of galactopoiesis during early lactation (Bell, 1995). Despite this, hypophagia develops during the last weeks of pregnancy and persists into early lactation driving energy balance to a substantially negative state (**Figure 1**; Bell, 1995; Rhoads et al., 2004). Decreased DMI prior to parturition is

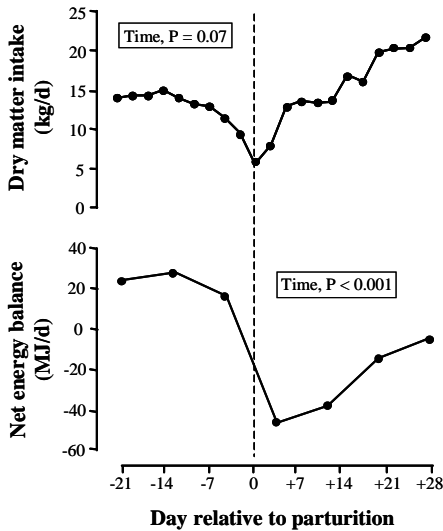


Figure 1. Profiles of dry matter intake and net energy balance during the transition period. Nine multiparous dairy cows were studied in the period from 3 wk prepartum to 4 wk postpartum (wk -3 to +4 relative to parturition). Day of parturition is denoted by the dashed vertical line. Figure adapted from Rhoads et al., 2004.

most likely caused by a combination of factors, including the metabolic and endocrine changes that occur during late pregnancy (Grummer, 1995; Ingvartsen and Andersen, 2000). Dry matter intake reaches a nadir at calving and slowly recovers thereafter (**Figure 1**; Grummer, 1995; Rhoads et al., 2004). The rate at which postpartum intake increases can be affected by a number of factors, including (but not limited to) diet composition, parity, body condition score and disease (Ingvartsen and Andersen, 2000; Jorritsma et al., 2003). Periparturient changes in digestion and metabolism further complicate nutrient availability. The onset of lactation is associated with hypertrophy of the digestive tract and increased capacity for nutrient absorption. These changes increase the utilization of the nutrients contained in the feed (Bauman and Currie, 1980) and may partially compensate for hypophagia that occurs during the periparturient period.

Depression in the concentrations of plasma insulin and glucose mirror the development of negative energy balance (**Figure 2**; Block et al., 2001; Rhoads et al., 2004). In contrast, concentrations of circulating GH and non-esterified fatty acids (NEFA)

rise during the periparturient period (Figure 2; Block et al., 2001; Rhoads et al., 2004). Despite elevated plasma GH, dairy cows experience a substantial reduction (approximately 70%) in plasma IGF-I between late pregnancy and early lactation (Figure 2; Vicini et al., 1991; Block et al., 2001; Rhoads et al., 2004). Perturbations in the metabolic transition around the time of calving can result in metabolic diseases that affect the well-being, productivity and reproductive performance of the dairy cow (Goff and Horst, 1997).

Reduced GH-Dependent Milk Production Responses in Early Lactation

The actions of GH are thought to be particularly important in preserving the metabolic homeostasis of the energy deficient early lactation dairy cow (Bell and Bauman, 1997; Bauman, 2000). Physiological effects of GH result from activation of the GH receptor (direct actions) or from GH-dependent stimulation of IGF-I synthesis (indirect actions; Le Roith et al., 2001). Examples of direct actions include promotion of NEFA export from adipose tissue by accentuating the lipolytic response to β -adrenergic signals and by inhibiting insulin mediated lipogenesis and glucose utilization (Bauman and Vernon, 1993; Etherton and Bauman, 1998). A second target of GH is skeletal muscle where it decreases glucose utilization and may favor export of amino acids by inducing insulin resistance (Bauman and Vernon, 1993; Bell and Bauman, 1997). Direct actions, such as these, provide the mammary gland critical precursors for milk synthesis by sparing non-mammary tissue use (Bell, 1995; Bauman, 2000).

Growth hormone is also the most potent positive signal regulating plasma IGF-I, a peptide hormone secreted predominantly by liver (LeRoith et al., 2001). Traditionally, the indirect actions of GH were believed to be mediated by IGF-I in both endocrine and autocrine/paracrine modes (Bauman and Vernon, 1993; Le Roith et al., 2001). A series of experiments have questioned the importance of plasma IGF-I and challenged the validity of a role for endocrine IGF-I. In these studies, liver-specific IGF-I deficient (LID) mice have significantly reduced circulating concentration of IGF-I (~75% reduction), but exhibit normal postnatal growth and development (Yakar et al., 1999; Sjogren et al., 1999). However, it may be premature to conclude from these studies that serum IGF-I is not essential for postnatal growth. By reducing circulating IGF-I further (~85%), Yakar et al. (2002) demonstrated that a threshold level of plasma IGF-I is required for normal body growth and bone development.

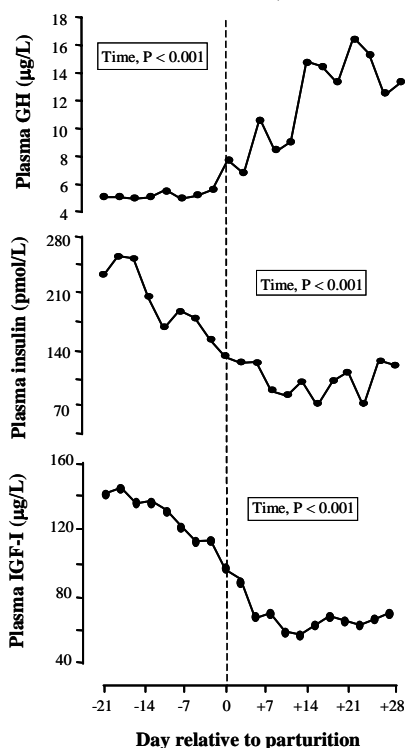


Figure 2. Profiles of plasma GH, insulin and IGF-I during the transition period. Nine multiparous dairy cows were studied in the period from 3 wk prepartum to 4 wk postpartum (wk -3 to +4 relative to parturition). Day of parturition is denoted by the dashed vertical line. Figure adapted from Rhoads et al., 2004.

Early lactation cows exhibit a blunted galactopoietic response and plasma IGF-I concentrations fail to normalize following administration of rbST (Richard et al., 1985; Vicini et al., 1991; Bauman, 1999). Similar galactopoietic responses to bST as well as an uncoupled GH-IGF axis (high plasma GH and low plasma IGF-I) are hallmarks of undernourished lactating dairy cows (McGuire et al., 1995). Mammary epithelial cells possess IGF-I receptors, the functionality of which has been demonstrated in metabolic and cell proliferation assays (Shamay et al., 1988; Dehoff et al., 1988; Collier et al., 1993; Hadsell et al., 2002). Further, close-arterial infusion of IGF-I in lactating goats results in increased milk synthesis and secretion from the mammary gland (Prosser et al., 1990; 1994). Although the growth hormone receptor (GHR) has been detected in mammary epithelial cells by *in situ* hybridization and immunohistochemistry (Sinowatz et al., 2000; Plath-Gabler et al., 2001), radio-receptor assays fail to detect significant specific GH binding in the bovine mammary gland (Akers, 1985; Collier et al., 1993). Together with the low level of IGF-I gene expression in mammary epithelial cells (Plath-Gabler et al., 2001), these results suggest that GH may not act directly or indirectly through autocrine/paracrine IGF-I to affect mammary gland function. These observations suggest that during states of negative energy balance the impaired plasma IGF-I response may underlie reduced GH-dependent milk production.

GHR Regulation During the Transition Period

The upstream regulatory region of the bovine GHR gene contains three promoters, termed P1, P2 and P3 (Lucy et al., 2001). They initiate transcription from exon 1A (promoter P1), exon 1B (promoter P2) and exon 1C (promoter P3; Lucy et al., 2001). The unique exons 1A, 1B and 1C are spliced onto a common core transcript of exons 2-10, giving rise to three major classes of transcripts referred to as GHR1A, GHR1B and GHR1C (Lucy et al., 2001). In addition, multiple transcription start sites were mapped in promoter P2 and P3 (Jiang and Lucy, 2001b). As a result, nine GHR transcripts were identified in cattle (Heap et al., 1996; Jiang et al., 1999; Jiang and Lucy, 2001b). Significantly, all GHR transcripts encode an identical GHR protein due to the common core transcript present in each.

Expression of the GHR1A transcript appears to be restricted to liver where it accounts for approximately half of the total abundance of GHR mRNAs (Lucy et al., 1998). The liver-enriched transcription factor hepatocyte nuclear factor-4 (HNF-4) has been shown to activate promoter P1, consistent with liver-specific presence of GHR1A (Jiang and Lucy, 2001a). In contrast, the GHR1B and 1C transcripts occur in all GH-responsive tissues including liver (Jiang et al., 1999; Jiang and Lucy, 2001b). GHR1B and GHR1C accounts for 39% and 11% of all GHR transcripts in liver and approximately 67% and 21% of all GHR transcripts in muscle, respectively (Jiang et al., 1999; Jiang and Lucy, 2001b). Ubiquitous presence of GHR1B and GHR1C transcripts may relate to structural features of promoters P2 and P3, such as absence of a TATA box, and activation by ubiquitous transcription factors, such as SP1 (Adams, 1999; Jiang et al., 2000). While GHR1B constitutes a large percentage of the GHR transcripts in tissues, such as liver and muscle, its overall importance is still uncertain because it is poorly translated *in vitro* (Jiang and Lucy, 2001b).

Reduced GH-dependent IGF-I production by the liver is one potential mechanism accounting for the decline in plasma IGF-I concentration during the transition period. Indeed, abundance of the liver specific GHR1A transcript is reduced by over 50%

immediately surrounding parturition. Data suggest that in cows with a “normal” transition the levels of this transcript normalize within a few weeks following parturition (Kobayashi et al., 1999; Radcliff et al., 2003b). However, anecdotal evidence indicates that diseases during the transition period can delay the recovery of the GHR1A mRNA (Lucy et al., 2001). During the periparturient period, abundance of the other GHR transcripts, representing mostly the GHR1B and 1C variants, remain unchanged (Lucy et al., 2001). Abundance of the GHR, measured directly or by radio-receptor assay, is reduced in a parallel manner with the GHR1A transcript (Radcliff et al., 2003a; Kim et al., 2004). These results are consistent with a model whereby GHR1A expression accounts for variation in GHR abundance and GH-dependent responses such as hepatic IGF-I synthesis (Radcliff et al., 2003a; Radcliff et al., 2003b; Kim et al., 2004).

The basis for reduced abundance of GHR1A mRNA and the GHR protein in early lactation has been examined in recent experiments. Based on the hypothesis that hypoinsulinemia during the transition period may be responsible for reductions in the GHR1A transcript and GHR levels, hyperinsulinemic-euglycemic clamps were performed in late-pregnancy and early lactation. Insulin appears to be a strong regulator of GHR1A mRNA and GHR protein as each parameter was increased or restored in late-pregnancy and early lactation, respectively (Butler et al., 2003; Rhoads et al., 2004). Significantly, hepatic IGF-I expression and plasma IGF-I were elevated during hyperinsulinemia indicating an increase in hepatic IGF-I production (Butler et al., 2003; Rhoads et al., 2004). It is unclear whether the increase in hepatic IGF-I production is due to a direct effect of insulin on IGF-I gene expression, mediated by a restoration of the GH-IGF axis or the sum of both. Regardless, it is clear that changes in GHR1A during parturition or in response to insulin are not mediated by variation in the abundance of HNF-4 (Kim et al., 2004; Rhoads et al., 2004). In an effort to mimic the hormonal environment of the periparturient dairy cow, Kobayashi et al. (1999; 2002) found no effect of stress (epinephrine) or reproductive (progesterone and estradiol) hormones on GHR1A expression. Despite these recent efforts, the mechanisms underlying poor GHR1A expression and low GHR protein abundance in early lactation cows remains poorly understood.

Roles of GH and IGF-I in Reproduction

Over the past several decades, the reproductive performance of dairy cattle has declined as milk production has increased (Butler, 2000; Lucy et al., 2001), thus affecting the profitability of the dairy industry. Decreasing reproductive performance may be related to the metabolic and nutritional demands of high levels of milk production. Despite extensive research in this area, little is known about how nutritional and metabolic signals are conveyed to the reproductive system. The GH/IGF-I system is a prime candidate for the metabolic regulation of reproduction because this system is disrupted during the periparturient period (and during undernutrition) and has been implicated in a number of reproductive processes that are critical to reproductive success. In addition, the mRNAs for GHR, IGF-I and the IGF-I receptor are found throughout the female reproductive tract, indicating potential roles for the GH/IGF-I system in the establishment and/or maintenance of pregnancy.

The processes of ovarian follicular development and selection are regulated by the GH/IGF-I system. When administered at levels that increased plasma IGF-I concentrations, exogenous GH increased the number of ovarian follicles (small and medium-sized) in cattle (Kirby et al., 1997; Gong, 2002). However, administration of GH at doses that did not increase circulating IGF-I had no effect on ovarian follicular population

(Gong et al., 1997). Furthermore, IGF-I treatment stimulated proliferation and the steroidogenic capacity of bovine granulosa cells *in vitro*, while GH had no effect (Gong et al., 1993). Therefore, early follicular development and steroidogenesis appear to be primarily mediated by IGF-I concentrations (which decrease during the periparturient period). As the follicle matures from the primary through the tertiary stages, the greatest abundance of GHR mRNA and protein shifts from the oocyte to the cells of the cumulus oophorus (Kolle et al., 1998). However, evidence suggests that GH plays little more than a supportive role during late follicular development (Kirby et al., 1997; Chase et al., 1998).

Members of the IGF-I family are found in both the granulosa and theca interna cells of the ovarian follicle. The mRNA for IGF-I is found primarily in granulosa cells and increases from early to mid-dominance (Yuan et al., 1998; Schams et al., 2002). The IGF-I receptor, which is responsible for mediating the cellular effects of endocrine, paracrine and autocrine IGF-I, is found in low levels in both the granulosa and theca interna cells of small follicles (Armstrong et al., 2000; Schams et al., 2002). Receptor expression increases in both cell types as follicles mature (Schams et al., 2002).

The IGF system plays a number of important roles in the growth and development of ovarian follicles. Traditionally, the synergistic interaction between IGF and the gonadotropins has been considered the most important role. Together, the gonadotropins and the follicular IGF system amplify the steroidogenic capacity of the ovarian follicle, thereby hastening the maturation process. Ovarian IGF-I is synthesized and secreted by the granulosa cells (Lucy, 2000). The IGF-I binds to its local receptor and increases the expression of the gonadotropin receptors as well as the activity of the second messenger systems activated by the gonadotropins. In turn, the gonadotropins increase ovarian IGF-I synthesis, as well as IGF-I receptor expression (Lucy, 2000). Thus, IGF-I is intricately involved in follicular steroidogenesis and development.

Evidence suggests that, in addition to synergistic interactions with the gonadotropins, the follicular IGF system plays an important role in dominant follicle selection. The concentration of IGF-I mRNA is higher in the dominant follicle than in subordinate follicles. Furthermore, subordinate follicles have higher concentrations of IGFBP-2 than the dominant follicle, suggesting that much of the IGF-I present in the subordinate follicles may not be available to activate the IGF-I receptor or initiate the cascade of synergistic events involving IGF-I and the gonadotropins (Yuan et al., 1998). Therefore, perturbations in the GH/IGF-I system during the periparturient period may be capable of affecting dominant follicle selection and steroidogenesis.

Interestingly, the CL contains the greatest abundance of GHR mRNA relative to other female reproductive tissues (Kirby et al., 1996). The GHR is restricted to the large luteal cells of the CL (Lucy et al., 1993; Yuan and Lucy, 1996; Kolle et al., 1998). Growth hormone receptor mRNA increases during the early luteal period and reaches maximal concentration during the functional luteal period (Schams et al., 1999). During luteolysis, the expression of GHR mRNA steadily declines (Neuvians et al., 2003). The effects of GH on CL development and function are unclear because it is difficult to distinguish the direct effects of GH from those of IGF-I. The weight of the CL in hypophysectomized ewes is restored to nearly normal levels when exogenous LH and GH are administered (Juengel et al., 1997). However, cattle with high circulating concentrations of GH and low IGF-I (due to a GH mutation or undernutrition) have smaller CL than control animals (Vandehaar et al., 1995; Chase et al., 1998; McCormack et al., 2004). Thus it appears that circulating IGF-I concentrations are critical for normal CL development.

The mRNA for IGF-I and the IGF-I receptor are found in the bovine CL (Perks et al., 1999). However, patterns of IGF-I and IGF-I receptor expression are not clearly defined. For instance, some have reported an increase in luteal IGF-I mRNA from day 5 to day 10 of the estrous cycle and an even greater IGF-I mRNA concentration in the regressing CL (Woad et al., 2000), while others have found constant levels of luteal IGF-I expression (Neuvians et al., 2003). Despite conflicting results regarding IGF-I and IGF-I receptor expression, there is general agreement that the luteal IGF system is important for the maintenance, function and perhaps the regression of the CL.

Within the bovine uterus, GHR mRNA is found in both the endometrium and myometrium (Kirby et al., 1996). There is limited information concerning the direct effects of GH on the bovine uterus. However, studies with ewes indicate that GH may enhance embryo survival by increasing the amount of tissue available to produce the uterine secretions necessary for pre-implantation embryo development (Jenkinson et al., 1999; Spencer et al., 1999).

The expression of IGF-I mRNA in the bovine uterus is at least partially localized to a band of dense caruncular stroma underling the luminal epithelium (Wathes et al., 1998) and the intercaruncular endometrial tissue (Pershing et al., 2002). Secretion of IGF-I into the uterine lumen peaks at estrus in response to high estradiol concentrations in both the bovine and ovine species. Therefore, uterine IGF-I concentrations are maximal several days before the embryo enters the uterus (Wathes et al., 1998). The IGF-I receptor is mainly expressed in the epithelium of the endometrial glands, but has also been identified in the caruncles and myometrium. Insulin-like growth factor I receptor mRNA concentrations are highest during the mid-luteal phase in the bovine and do not appear to be influenced by estradiol or progesterone concentrations (Wathes et al., 1998). However, this does suggest that the uterus is most responsive to circulating IGF-I concentrations after the embryo has entered the uterus and prior to the maternal recognition of pregnancy.

Reproductive Effects of the IGF System in Cattle

Cattle with low circulating concentrations of IGF-I due to nutrient restriction or during a period of negative energy balance typically exhibit disrupted reproductive processes (especially follicular development). Beef and dairy cows with low circulating IGF-I concentrations experienced extended postpartum intervals to first ovulation (Beam and Butler, 1997; Roberts et al., 1997; Zulu et al., 2002; Diskin et al., 2003). And likewise, ovulation of the first postpartum dominant follicle in dairy cattle was associated with higher IGF-I concentrations the first two weeks after calving (Beam and Butler, 1997). The delay in ovulation during periods of undernutrition is likely due to decreased follicular responsiveness to LH (perhaps due to lack of synergistic effects of IGF-I), decreased GnRH secretion and decreased LH secretion. As a result, estradiol production is suppressed to levels that are unable to stimulate the preovulatory GnRH surge. Thus, undernutrition and negative energy balance (and the associated decrease in circulating IGF-I concentrations) inhibit the LH secretion necessary to support follicle development in addition to decreasing the ability of the follicle to respond to LH. Together, these mechanisms result in sustained and extended anestrus periods.

Conclusions

During the transition period, dairy cattle are particularly susceptible to metabolic and infectious diseases that affect the ease with which they transition from the dry period

into lactation. Importantly, the transition dairy cow exhibits discordant changes in the GH/IGF-I axis (i.e. elevated concentrations of plasma GH and depressed concentrations of circulating IGF-I). Deviations in cow health during the transition period slow the recovery of the GH/IGF-I axis during the postpartum period, and may negatively impact subsequent productivity and reproductive performance. The weak GH-dependent milk yield response indicative of early lactation may be a function of the inability of exogenous GH to increase GH-dependent hepatic IGF-I production. A similar mechanism may underlie the reduced reproductive competency typical of early lactation. However, because the GH/IGF-I system is involved in nearly every aspect of the bovine reproductive process it is difficult to discern between systemic and local effects of the GH/IGF-I axis on fertility. If GH exerts direct effects on reproductive tissues via locally produced IGF-I it may be reasonable to hypothesize that the components of the GH/IGF-I system in reproductive tissues may be regulated by factors, such as negative energy balance, during early lactation. Further investigations into the mechanisms underlying dysfunctional GH responsiveness in liver as well as other tissues may provide crucial details for the improvement of transition dairy cow production and performance.

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