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Mechanisms linking the somatotropic axis with insulin: Lessons from the postpartum dairy cow

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ABSTRACT

Growth hormone (GH; synonymous with somatotropin) coordinates nutrient partitioning in dairy cattle by increasing glucose synthesis in liver and mobilizing lipid from adipose tissue. The effects of GH are opposite to the glucose-clearing effects of insulin. It is not surprising, therefore, that physiological mechanisms have evolved which coordinate the actions of both hormones. There appears to be direct communication between the somatotropic axis and the insulin axis. The manifestation of this interaction is clearly evident in postpartum dairy cows where blood GH concentrations are high and blood insulin concentrations are low. Diabetic states in humans [either type 1 diabetes mellitus (insulin-dependent) or type 2 diabetes mellitus (insulin resistance)] also lead to abnormal function within the somatotropic axis; evidence that insulin and GH are closely linked in humans. Cattle and humans share common elements of somatotropin physiology perhaps because common regulatory mechanisms control the expression of key genes within the axis of each species. This review will discuss the mechanisms linking insulin and somatotropin in cattle and humans. Similarities between diabetic states in humans and low-insulin states in postpartum cows will be highlighted.

Keywords: growth hormone; IGF-I; insulin; diabetes; cow; lactation.

INTRODUCTION

The initiation of lactation and the metabolic transition to peak milk production occurs rapidly in dairy cattle (Bell, 1995). The rapid increase in nutrients required for lactation causes a negative energy balance during the early postpartum period that may last for several weeks after calving. Blood glucose concentrations are low during this period because the mammary gland uses glucose for energy and the synthesis of lactose. Indeed, over 3 kg of pure glucose may be required daily for cows in peak lactation. This is remarkable given the fact that cows are ruminants and very little glucose escapes the rumen. Low glucose concentrations in postpartum cows are associated with low blood insulin concentrations. There also appears to be insulin resistance during this period; particularly in high producing dairy cows. Low insulin concentrations and partial insulin resistance redirect existing glucose pools to the mammary gland where glucose uptake is independent of blood insulin.

The presence of low blood insulin and insulin resistance in postpartum cows creates a natural link between the endocrine physiology of postpartum cows and the physiology of diabetic states found in humans [type 1 diabetes mellitus (insulin-dependent) or type 2 diabetes mellitus (insulin resistance)]. Indeed, a number of parallels can be drawn between each condition and the biology of the postpartum cow (Table 1). In either case, the principle distinguishing feature is that postpartum cows have relatively low blood glucose; and thus, cows do not

possess the central clinical feature of diabetes mellitus in humans (elevated blood glucose concentrations).

TABLE 1: Metabolic and endocrine comparison of diabetic states in humans with the normal state of the early postpartum dairy cow. Low, high, or normal refers to levels that are relative to a human control (type 1 and type 2 diabetes) or a non-lactating cow. Data are summarized from the scientific literature (Bereket *et al.*, 1999; Frystyk *et al.*, 1999; Radcliff *et al.*, 2003).

	Type 1 diabetes	Type 2 diabetes	Postpartum cow
Blood insulin	Low	High	Low
Insulin sensitivity	Low	Low	Low
Blood glucose	High	High	Low
Blood GH	High	Low	High
Blood IGF-I	Low	Normal	Low
Liver GHR	Low	High	Low

The relationship between blood insulin and blood growth hormone (GH) is important because each hormone affects lactation in an opposite way. High producing cows have high blood GH concentrations, low blood glucose concentrations, and low blood insulin concentrations (Bauman, 1999). The high blood GH concentrations promote adipose tissue mobilization and increase blood nonesterified fatty acids (NEFA) concentrations. The NEFA can be used for milk fat synthesis. Low blood insulin concentrations redirect blood glucose toward the mammary gland (mentioned above). Low producing cows

have lower blood GH and higher blood insulin concentrations. Their capacity to mobilize NEFA is less and more glucose is partitioned to tissues outside the mammary gland. These features lead to lower milk production.

This review will examine the endocrine mechanisms for nutrient partitioning in dairy cattle. Growth hormone and insulin physiology will be reviewed. New discoveries reported in the human literature will be used to develop a model for GH/insulin interactions in postpartum cows.

NUTRIENT PARTITIONING IN DAIRY CATTLE

Blood GH concentrations increase shortly after calving (Bauman, 1999). Greater blood GH is believed to coordinate nutrient partitioning; the process through which nutrients are preferentially targeted for milk production (Etherton and Bauman, 1998). Multiple tissues are affected by GH in the lactating cow but coordinated events in liver and adipose tissue may be most important. In liver, the postpartum increase in GH stimulates gluconeogenesis. The increase in gluconeogenesis is believed to involve a direct effect of GH on the gluconeogenic pathway as well as an indirect effect of GH through an antagonism of insulin action. The actions of GH on liver gluconeogenesis in periparturient dairy cattle are essential for meeting glucose demands for milk production. In adipose tissue, GH increases lipolysis which in turn increases blood NEFA concentrations. The NEFA may be oxidized in liver or extra-hepatic tissues or may be incorporated directly into milk fat.

Growth hormone acts through a cell surface receptor. Although the GH receptor (GHR) is found in most tissues, the greatest concentrations of GHR are in liver (Lucy *et al.*, 2001). The second most-abundant location for GHR is adipose tissue. In liver, GH turns on a variety of genes by activating the Jak-Stat intracellular signaling system (Herrington & Carter-Su, 2001). Perhaps the most widely known response to GH in liver is the increase in the synthesis and secretion of insulin-like growth factor-I (IGF-I) (LeRoth *et al.*, 2001). Insulin-like growth factor-I acts as an endocrine hormone that controls GH secretion through a negative feedback loop.

GROWTH HORMONE RECEPTOR EXPRESSION IN POSTPARTUM COWS

The GHR gene in cattle is structurally related to the GHR gene in humans. Three GHR promoters have been characterized in cattle (P1, P2, and P3) that transcribe three GHR mRNA variants (1A, 1B, and 1C respectively) (Lucy *et al.*, 2001). The mRNA variants arise from the alternative splicing of different exon 1 onto exons 2 through 10 of the bovine GHR mRNA. Although the mRNA are different in exon 1, the receptor protein is the same because the GHR protein is encoded in exons 2 through 10 of the mRNA. The primary location for GHR 1A mRNA is the liver of

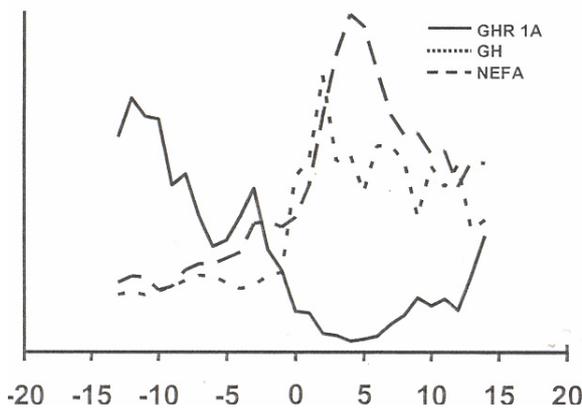
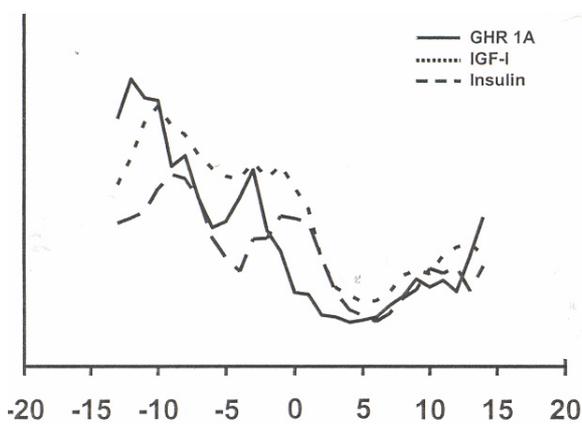
adult animals. The GHR 1A mRNA is unique because the mRNA amount is regulated by nutrition, development, and physiological state. Most of the physiological aspects of GHR 1A in cattle are similar to the module B GHR variants in humans (Goodyer *et al.*, 2001). There is considerable DNA sequence homology within this region suggesting that homologous elements control liver GHR expression in each species. Hepatocyte nuclear factor 4 (HNF-4) is a liver-enriched transcription factor that binds GHR P1 and increases GHR 1A expression (Jiang & Lucy, 2001). Thus, the liver specificity of GHR 1A mRNA may be partially explained by transcription factor binding sites in the proximal promoter region. The GHR P2 transcribes GHR 1B mRNA. The GHR P2 is active in a wide variety of tissues. Developmental or nutritional regulation of GHR P2 in liver has not been observed in cattle. The GHR P3 transcribes GHR 1C mRNA and its activity is similar to GHR P2. The GHR 1B and 1C transcripts are physiologically similar to module A variants in humans (Goodyer *et al.*, 2001). Expression of GHR 1B, GHR 1C, and human module A variants are controlled by ubiquitously expressed transcription factors. Thus, the low-level of GHR in a variety of tissues can be explained by the ubiquitous nature of these regulatory factors.

A series of physiological events involving GH, GHR, IGF-I, and insulin coordinate metabolic events during early lactation in cattle. The GHR 1A mRNA in liver decreases about 2 days before calving, remains low for approximately one week, and slowly increases during the second week after calving (Figure 1; Radcliff *et al.*, 2003). The decrease in GHR 1A mRNA after calving is associated with a decrease in the specific binding of GH to liver membranes and the GH-refractory period of early lactation. The profile for liver IGF-I is similar to GHR 1A but the decrease in IGF-I occurs slightly later than the decline in GHR 1A mRNA. The delay may reflect the dependence of liver IGF-I on GHR 1A. Blood insulin concentrations decrease as well during the periparturient period. The decrease in insulin occurs about 2 to 3 days after the decrease in GHR 1A mRNA and coincides with the decrease in IGF-I. Blood GH concentrations increase during the first week after calving perhaps because blood IGF-I concentrations decrease and negative feedback on GH is reduced. The increase in blood GH causes lipid mobilization and elevated blood NEFA (Figure 1). Remarkably, the signal that initiates adipose tissue mobilization (decreased GHR 1A) occurs coincident with lactogenesis and well before peak milk production. Thus, mechanisms for nutrient partitioning are triggered ahead of the major nutrient demand for lactation (a feed-forward system).

The decrease in GHR 1A is a phenomenon that is unique to dairy cattle because beef cattle do not undergo the same changes in GHR 1A around calving (Jiang *et al.*, 2004). Something must cause the large decrease in GHR 1A mRNA that occurs immediately before calving. A variety of hormonal and metabolic events occur during this

period (Bell, 1995). The changes in GHR 1A for dairy versus beef may be a consequence of differential sensitivity to periparturient hormones within beef and dairy breeds or may be a consequence of greater lactogenic drive in dairy cows. The respective roles that parturient signals and lactogenic signals play in controlling GHR 1A needs to be clarified.

FIGURE 1: Relative amounts of liver GHR 1A mRNA, blood insulin, and blood IGF-I (upper graph) and liver GHR 1A, blood GH, and blood NEFA (lower graph) in postpartum dairy cows sampled for 15 days before through 15 days after parturition. Data are smoothed means from the original data published by Radcliff *et al.* (2003).



MECHANISMS CONTROLLING GHR 1A mRNA EXPRESSION

The decrease in GHR 1A before calving causes the “uncoupling” of the somatotropic axis in postpartum cows. There is a subsequent “recoupling” of the somatotropic axis during early lactation. The recoupling process has been linked to postpartum nutrition and energy balance and is probably dependent on GHR 1A (Radcliff *et al.*, 2004).

If postpartum nutrition and energy balance affects recoupling (GHR 1A expression) then what is the nature of the signal? Insulin infusion into early postpartum dairy cows increased liver GHR 1A mRNA (Butler *et al.*, 2003). The stimulatory effect of insulin on liver GHR is also observed in humans and other species (Bereket *et al.*, 1999). Insulin increases the activity of liver-specific transcription factors including HNF-4 (Kulkarni & Kahn, 2004). Greater expression of GHR 1A following insulin treatment, therefore, may be secondary to an increase in HNF-4 in liver. The uncoupling of GHR 1A immediately before calving may not be insulin-dependent because GHR 1A mRNA decreases before the decrease in blood insulin (Figure 1). The coincident increase in blood insulin and liver GHR 1A mRNA, however, suggests that the recoupling process depends on insulin.

Blood IGF-I concentrations are decreased in type 1 diabetes mellitus and there is a marked elevation in blood GH (Bereket *et al.*, 1999). The increase in GH can complicate clinical management of the disease because of the antagonistic relationship between GH and insulin signaling (Dominici & Turyn, 2002). The uncoupling of GH and IGF-I in type 1 diabetes is believed to be a consequence of reduced GHR expression (evidenced by low GH binding protein in type 1 diabetic patients; Bereket *et al.*, 1999). Thus in humans and cattle, low insulin leads to low GHR expression, decreased blood IGF-I, greater blood GH, and insulin resistance (perhaps secondary to elevated GH). Pathology does not occur in cattle because blood glucose concentration remains low in the lactating animal (via glucose clearance by the mammary gland).

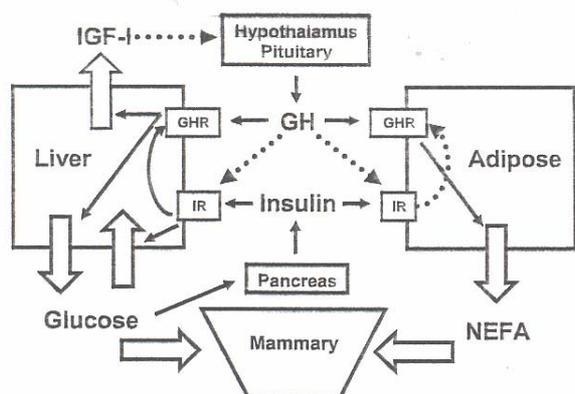
UNIQUE ASPECTS GHR EXPRESSION IN ADIPOSE TISSUE

Growth hormone receptor expression in liver and adipose tissue is controlled by different promoters. Different promoters can potentially direct tissue-specific responses for GHR expression. The physiological importance of tissue-specific GHR expression was demonstrated recently when it was discovered that insulin had opposing effects on GHR expression in liver and adipose tissue (Butler *et al.*, 2003). In response to insulin, GHR 1A and IGF-I expression increased in liver. The effects of insulin infusion on adipose tissue, however, were completely opposite because insulin infusion decreased GHR and IGF-I expression in adipose tissue. The opposing effects of insulin on GHR 1A (liver) and GHR 1B/1C (adipose tissue) encode a unique physiological mechanism. When insulin concentrations are high, blood GH concentrations decrease (via greater IGF-I negative feedback), adipose GHR concentrations decrease, and, as a consequence, lipid mobilization decreases. When insulin concentrations are low, blood GH concentrations increase (via less IGF-I negative feedback), adipose GHR concentrations increase, and lipid mobilization increases.

A MODEL FOR GH AND INSULIN INTERACTIONS DURING LACTATION

The aforementioned effects of insulin on GHR and IGF-I expression can be combined with recent data on type 1 and type 2 diabetes mellitus to create a model for early lactation. The model includes the hypothalamus/pituitary, liver, pancreas (β cell; insulin source), adipose tissue, and the mammary gland. The GHR decreases in liver shortly before calving. The decrease in GHR leads to a decrease in liver IGF-I synthesis and a decrease in blood IGF-I concentrations. The decrease in blood IGF-I causes reduced negative feedback on GH and an increase in blood GH concentrations. Greater blood GH increases liver gluconeogenesis and promotes lipolysis in adipose tissue. Insulin concentrations decrease during this period because glucose concentrations are low. Low insulin concentrations keep liver GHR 1A expression low. The decrease in insulin, however, has an opposite effect on adipose tissue where GHR expression increases in response to a decrease in blood insulin. The biological mechanism controlling the adipose tissue response is unclear. The increase in GHR increases the responsiveness of adipose tissue to GH and enhances lipid mobilization. Elevated GH and elevated NEFA during this period antagonize insulin action and create a state of insulin resistance (Dominici & Turyn, 2002; Klover & Mooney, 2004). The low blood insulin and insulin resistance blunt glucose utilization by non-mammary tissues and conserve glucose for milk synthesis.

FIGURE 2: Model for the interaction of growth hormone (GH) and insulin in postpartum dairy cows. Solid lines infer stimulatory actions. Broken lines infer negative feedback or inhibitory actions. See text of details of the model. GHR = growth hormone receptor. IR = insulin receptor.



The cycle described above (low liver GHR, low IGF-I, high GH, low glucose, low insulin, and insulin resistance) is gradually turned off during the first 4 to 8 weeks of

lactation. The critical event may be an increase in blood glucose. The increase in blood glucose occurs when glucose synthesis exceeds glucose demand. Greater blood glucose increases blood insulin concentration; the increase in insulin increases liver GHR and liver IGF-I; the increase in blood IGF-I concentrations feeds back negatively on GH; and the decrease in GH reduces adipose tissue mobilization. The increase in insulin also decreases adipose tissue GHR and reduces adipose tissue responsiveness to GH. The link between the insulin and somatotropin systems, therefore, insures a coordinated response to changing nutrient demand and availability during early lactation.

CONCLUSIONS

The physiology of postpartum dairy cows and the physiology of diabetic states in humans share common features. Type 1 diabetes is a condition characterized by low insulin. Type 2 diabetes is caused by insulin resistance. Both low insulin and insulin resistance are found in postpartum cows. The high blood GH concentrations that are characteristic of high producing dairy cattle can be linked to low blood insulin during early lactation. The insulin resistance in postpartum cows may be linked to high blood GH concentrations. The pathological consequences of type 1 and type 2 diabetes in humans are caused by high blood glucose. Postpartum cows do not experience these pathologies because the mammary gland consumes large quantities of glucose for milk production. Thus, endocrine characteristics that create a diabetic disease state in humans are advantageous to dairy cattle because greater glucose availability provides a critical substrate for milk synthesis.

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