ELSEVIER

Domestic Animal Endocrinology 17 (1999) 101–116

DOMESTIC
ANIMAL
ENDOCRINOLOGY

Bovine somatotropin and lactation: from basic science to commercial application

D.E. Bauman

Department of Animal Science, Cornell University, Ithaca, NY 14853-4801, USA

Received 5 February 1999; accepted 5 February 1999

Abstract

Bovine somatotropin (bST) results in increased milk yield and an unprecedented improvement in efficiency. Beginning in the 1930s to present day, investigations have examined animal-related factors such as nutrition, bioenergetics, metabolism, health and well being and consumer-related factors such as milk quality, manufacturing characteristics, and product safety. Overall, bST is a homeorhetic control involved in orchestrating many physiological processes. Direct effects involve adaptations in many tissues and the metabolism of all nutrient classes—carbohydrates, lipids, protein, and minerals. Mechanisms include alterations in key enzymes, intracellular signal transduction systems, and tissue response to homeostatic signals. Indirect effects involve the mammary gland and are thought to be mediated by the insulin-like growth factor (IGF) system. Specific changes include increased cellular rates of milk synthesis and enhanced maintenance of secretory cells. Indirect effects are modulated by environment and management factors, especially nutritional status. This modulation is a central component in allowing ST to play a key role in regulating nutrient utilization across a range of physiological situations. U.S. commercial use began in 1994, and adoption has been extensive. From a consumer perspective, bST was unique, and special interest groups loudly predicted dire consequences. However, introduction of bST had no impact on milk consumption, and milk labeled as recombinant bST-free occupies a minor niche market. From a producer perspective, commercial use verified scientific studies and enhanced net farm income. Overall, ST is a key homeorhetic control regulating nutrient partitioning, and the ST/IGF system plays a key role in animal performance and well being across a range of physiological situations.

Keywords: Somatotropin; Lactation; Metabolism; Homeorhesis; IGF mechanisms

* Corresponding author. Tel.: +1-607-255-2262; fax: +1-607-255-9829.
E-mail address: deb6@cornell.edu (D.E. Bauman).

0739-7240/99/$ – see front matter
PII: S0739-7240(99)00028-4

1. Introduction

In the 1920s, it was discovered that a crude extract isolated from bovine pituitaries stimulated growth of rats [1]. This extract was referred to as "growth hormone" or "somatotropin" after the Greek derivation for tissue growth. However, it soon became apparent this crude extract did much more than stimulate growth; it also stimulated milk yield in pseudopregnant rabbits [2] and lactating goats [3]. Following these initial discoveries, the specific protein in the pituitary extract responsible for the galactopoietic response was identified as somatotropin (ST), and over the last 70 years the work has been extended to show that many, if not most, lactating mammals increase milk yield when treated with exogenous ST [4,5].

Many companies initiated programs to examine the application of biotechnology to the somatotropic axis. One of the first experimental products from the breakthroughs in biotechnology was recombinantly derived bovine somatotropin (bST), and this allowed for a dramatic increase in related investigations. Studies with recombinant bST have consistently demonstrated that treatment resulted in an unprecedented increase in milk secretion. The magnitude of the gain in efficiency of milk production was equal to that normally achieved over a 10- to 20-year period with artificial insemination and genetic selection technologies [6]. Thus, a major focus of the research has been related to evaluating the potential for commercial application in the dairy industry. A second focus of the investigations relates to understanding the biology and the role of ST in the regulation of nutrient use. These interests and the availability of bST resulted in studies by scientists around the world and the publication of several thousand scientific articles. As a consequence, bST is one of the most extensively investigated technologies in agriculture. Although commercial use of bST has been of importance to the economic return of dairy producers, the gains in knowledge of lactation biology also have been extraordinary and will be invaluable over the long term.

The following sections will review aspects of bST ranging from basic science to commercial application. Emphasis will be on an overall perspective and the development of concepts. Space constraints and topic limitations require that review citations be featured wherever possible.

2. Basic science

2.1. The early years

The early work with dairy cattle involved a number of pioneering groups. Among these were Asimov and Krouze [7], who examined the galactopoietic efficiency of crude anterior pituitary extract. These Russian scientists examined responses to bST in over 2000 cows and consistently observed that a single injection of pituitary extract induced a temporary increase in milk yield. These workers also made some cogent observations when they reported the "absolute harmlessness" of bST use and that responses were "more profitable on a well-run farm than on a farm with a poor food basis or where cattle are kept under unsatisfactory

conditions" [7]. Management quality remains a key feature of current extension recommendations to maximize economic return in the commercial use of bST.

Scientists in the U.K., led by Folley and Young, conducted an elegant series of studies to help alleviate chronic food shortages during the Second World War (for reviews, see refs. [8,9]). These investigations were the first to identify ST as the galactopoietic factor in the crude pituitary extract. They also established dose response curves and characterized many aspects of the response to exogenous bST. Among these were the demonstration that milk response was greatest during the declining phase of lactation, milk quality was not altered, and deleterious effects did not occur even when cows were pregnant. However, bST supply was limited to that isolated from the pituitary glands of slaughtered cows, and they found this inadequate to significantly impact their national milk supply, even though its use "would be highly profitable to the individual farmer" [9].

Somatotropin investigations during this era also were affected by the existing concepts of nutrient regulation. As described by Hammond [10], the prevailing view of the regulation of nutrient use throughout this period was one of "competition" between organs. According to this concept, increases in milk production were the result of either decreasing nutrient use by peripheral tissues so that more remained for mammary use or increasing the metabolic rate of the mammary gland so it would be in a position to "compete more successfully with other tissues of the body for nutrients in the blood stream" [10]. This concept of regulation as a competition between tissues can also be described as a push/pull concept.

Mechanisms for ST's actions were thought to involve acute effects, and most scientists favored the "push" concept. This involved altering metabolism of body tissues to reduce their competition, thereby allowing more nutrients to flow to the mammary gland for milk synthesis [10]. Specifically, these acute alterations were identified as a glycotropic activity (reduced response to insulin in glucose tolerance test), diabetogenic activity (hyperglycemia and glycouremia), and lipolytic activity (increased blood nonesterified fatty acids [NEFA]) [8,9,11–14]. Other scientists favored a pull concept suggesting that ST treatment might enhance mammary lobuloalveolar growth and activity, thereby allowing the mammary gland to compete more effectively for nutrients [15,16].

Based on the push/pull scenario, it was anticipated that the glycotropic, diabetogenic and lipolytic activities would cause metabolic problems in bST-treated cows [9,17,18]. This may explain why early studies tended to involve short term treatment, generally 1 day, and used low producing cows. Longer term treatment of high producing cows was expected to result in diabetes, excessive fat mobilization, ketosis, and burnout [9,17,18]. Nevertheless, during these early years, Brumby and Hancock [16] and Machlin [15] both conducted studies lasting 10–12 weeks that demonstrated increases in milk yield up to 40% with no adverse effects in the treated cows.

2.2. New concepts

In the late 1970s, the dogma on the mechanisms of action for ST were challenged by two groups—Hart and Bines at the National Institute for Research in Dairying and our group at Cornell. This re-evaluation was based on two lines of reasoning. First, it became clear that the physiological basis for improved efficiency of genetically superior cows related to

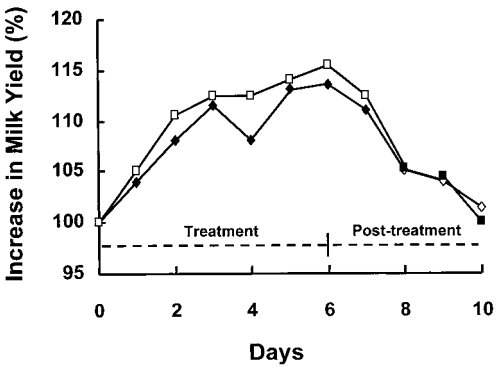

Fig. 1. First study conducted with recominantly derived bST in lactating cows. Comparison involved daily injections of 25 mg of recombinant bST (open square) or pituitary bST (closed diamond) for 6 days. Pretreatment milk yield averaged 32 kg/day. Adapted from Bauman et al. [23].

differences in the partitioning of absorbed nutrients [19–22]. Second, new concepts were proposed that explained nutrient regulation and suggested that ST was a homeorhetic control [19]. Key features were that homeorhetic controls operate on a "chronic" basis and involve a "coordination" of physiological processes and tissue metabolism. Indeed, daily administration of pituitary-derived bST to high producing dairy cows resulted in a marked increase in milk yield without any clinical or subclinical symptoms of diabetes, ketosis, or burnout. Today, somatotropin is arguably the best characterized of all homeorhetic controls, and the concept of homeorhesis has been applied to many physiological states.

When we first conducted studies with high producing dairy cows we were investigating the biology with no thought of a potential for commercial application. However, developments in biotechnology offered the opportunity to increase the bST availability, and in 1982, results from the first recombinantly derived bST were published [23]. The bST for this landmark study was produced jointly by Monsanto Co. and Genentech Inc., and the amount was sufficient for a 6-day study with four cows (Fig. 1). The first longer term study was reported in 1985. In this instance, there was sufficient recombinant bST for 188 days of treatment, and impressive increases in milk yield and productive efficiency were observed [24]. Thereafter, supply of bST and investigations increased exponentially and involved scientists around the world.

Dimensions of the production response to bST have been summarized in a number of reviews [6,25–29]. However, several general aspects were of special importance in the initial studies because they provided insight to bST's mechanism of action as well as its potential for commercial application. One of these was the effect of bST on bioenergetics of the cow. We conducted joint studies with the USDA Beltsville Energy Laboratory, and results demonstrated that energy expenditure for maintenance and the partial efficiency of milk synthesis were unchanged [30]. These results contrasted with thyroprotein studies, in which treatment resulted in a 20% increase in energy expenditure for maintenance and the synthesis of milk [6]. Stress or sickness results in an increase in energy expenditure, and the fact that maintenance requirement was not altered provided a clear indication that bST treatment had not adversely affected animal well being. Thus, productive efficiency gains with bST

represented a "dilution of maintenance" whereby a larger portion of consumed nutrients were used for milk synthesis [30,31].

Diet and intake were additional important considerations. The prevailing view was that intake limited performance; if this were correct, then bST-treated cows would require special, expensive diets formulated with a greater nutrient density to sustain the milk response. We had proposed the opposite and suggested that the rate of metabolic processes played a key role in regulating intake [19]. Results from longer term bST studies clearly demonstrated that cows increased their voluntary intake over the first few weeks to match nutrient needs for the increased milk yield. Thus, bST-treated cows required no special diets but merely needed the opportunity to consume adequate amounts of a balanced diet [27].

Another key aspect in the early studies was the effect of bST on the priority in nutrient use (for reviews, see refs. [27,28]). Results demonstrated that primiparous heifers that had not attained mature growth would still did so when treated with bST, but their milk response to bST will be decreased by an amount that matched the nutrient requirement for growth. Likewise, in bST-treated cows that were simultaneously lactating and pregnant, the priority in nutrient use shifted in the normal manner during the latter stages of pregnancy such that milk yield declined and nutrient use for fetal development and replenishment of body reserves increased.

Finally, effects on milk composition were particularly important. Results demonstrated that nutritional components and manufacturing characteristics of milk were not altered by bST treatment (for reviews, see refs. [6,32,33]). Milk composition is affected by many factors including genetics, stage of lactation, breed, diet, environment, and season, and these factors affected milk composition in an identical manner in bST-treated cows.

2.3. Whole-animal responses

Somatotropin alters the partitioning and use of absorbed nutrients with little or no effect on digestive processes [27,34]. Table 1 summarizes many of the physiological processes that are altered by ST treatment. It is apparent that effects involve an orchestration that includes many, if not most, physiological processes. The period when this coordination is most important is when bST treatment is initiated. The milk response is immediate and often represents a 10–40% increase whereas voluntary intake adjustment takes several weeks. Without these coordinated changes, metabolic problems would occur with the initiation of bST treatment, and these have never been observed.

The glucose economy is critical in a dairy cow and provides a clear example of the orchestrated responses to bST [4,26,34]. In a high producing cow, glucose is derived primarily via hepatic gluconeogenesis with the mammary gland using 60–85% of the total glucose turnover. With initiation of bST treatment, mammary uptake and use of glucose increase to match the increased milk synthesis. This is accommodated by changes in peripheral tissues, which include an increase in hepatic rates of gluconeogenesis, a reduction in muscle uptake of glucose, and a reduction in whole body oxidation of glucose [4,26,34, 35]. These coordinated changes in glucose production and utilization are essential to preserve

Table 1
Biological effects of somatotropin treatment during lactation[a]

Tissue	Physiological process affected
Mammary tissue	↑ synthesis of milk with normal composition
	↑ uptake of nutrients used for milk synthesis
	↑ activity per secretory cell
	↑ maintenance of secretory cells
	↑ blood flow consistent with change in milk synthesis
Adipose tissue	↓ lipid synthesis if in positive energy balance
	↑ lipolysis if in negative energy balance
	↓ glucose and acetate uptake & glucose oxidation
	↓ insulin stimulation of glucose metabolism and lipid synthesis
	↑ catecholamine stimulation of lipolysis
	↓ antilipolytic effects of adenosine and prostaglandins
Liver	↑ basal rates of gluconeogenesis
	↑ ability to synthesize glucose
	↓ ability of insulin to inhibit gluconegenesis
Kidney[b]	↑ production of 1,25 vit D_3
Intestine[b]	↑ absorption of Ca, P required for milk
	↑ ability of 1,25 vit D_3 to stimulate calcium binding protein
	↑ calcium binding protein
Muscle	↓ glucose uptake
Systemic effects	↓ glucose oxidation
	↓ glucose response to insulin tolerance test
	↑ NEFA oxidation if in negative energy balance
	↓ amino acid oxidation and blood urea nitrogen
	↑ circulating IGF-I, IGFBP-3, and acid labile subunit
	↓ circulating IGFBP-2
	↑ cardiac output consistent with increases in milk output
	↑ enhanced immune response
	NC energy expenditure for maintenance
	NC partial effciency of milk synthesis
	↑ voluntary intake to match nutrient needs for extra milk synthesis
	↑ productive efficiency (milk/unit of intake)
	↓ animal waste (fecal and urine output/unit of milk)

[a]Adapted from refs. 4, 6, and 34. Changes (↑ = increased, ↓ = decreased, NC = no change) that occur in initial period of bST supplementation when metabolic adjustments occur to match the increased use of nutrients for milk synthesis. With longer treatment, voluntary intake increases to match nutrient requirements.
[b]Demonstrated in nonlactating animals and consistent with observed performance in lactating cows.

glucose homeostasis during the transition and maintenance of a greater rate of milk synthesis. If glucose supply and use get out of balance, then hypoglycemia and ketosis would occur; the precision of the coordination is demonstrated by the fact that these metabolic disorders have never been reported with the initiation of bST treatment.

Somatotropin coordinates processes involving all nutrient classes—carbohydrate, protein,

lipid and minerals (Table 1). It also includes alterations in the mammary gland that result in greater rates of milk synthesis and an improved maintenance of mammary cell numbers [4,5,26]. This latter effect is the major factor in the improved lactation persistency observed with bST treatment. Overall, treatment with ST increases mammary uptake and use of milk precursors, while simultaneously altering the metabolism of other body tissues in a manner to support a greater use of nutrients for milk synthesis.

2.4. Cellular mechanisms

When we crystallized the concept that homeorhetic controls operate on a chronic basis to prioritize nutrient use, we emphasized it was still essential for homeostatic controls to function on an acute basis to maintain steady-state conditions [19]. To accommodate this, we proposed that mechanisms whereby homeorhetic controls alter physiological processes would involve alterations in tissue responses to homeostatic signals. Subsequent work has demonstrated that these are indeed the mechanisms, and several reviews have discussed them in detail [4,5,26,36]. The following are chosen to illustrate general concepts and mechanisms.

Adipose tissue and lipid metabolism provide examples to illustrate the mechanisms that allow ST to alter nutrient partitioning. Effects of ST on adipose tissue are direct, and treatment alters both lipogenesis and lipolysis with the net effect being related to energy balance [4,5]. If treatment is initiated when cows are in positive energy balance, adipose tissue changes involve a reduction in lipogenesis, whereas rates of lipolysis are enhanced if treatment occurs when cows are in negative energy balance. The biologic mechanisms that allow for these adaptations include changes in amounts of key enzymes and alterations in the signal transduction system for the homeostatic signals that acutely regulate lipogenesis and lipolysis.

Insulin is an important homeostatic control in the regulation of lipid metabolism. Treatment with bST reduces whole-body glucose response to insulin tolerance tests; this represents the glycotropic activity reported in early studies. This effect of ST is frequently referred to as “insulin resistance,” but this is misleading because the effect is clearly tissue-specific and relates to only a portion of the insulin-responsive processes. Specifically, the effect relates to an attenuation of insulin’s ability to stimulate lipogenesis in adipose tissue. In contrast, ST treatment does not reduce the ability of insulin to inhibit lipolysis, stimulate protein synthesis in adipose tissue, or stimulate glucose uptake and protein synthesis in muscle [4,5]. The most complete examination of the effect of ST on insulin has been with adipose tissue from pST-treated pigs. These results show that the reduced ability of insulin to stimulate lipogenesis involves a decrease in sensitivity (ED_{50}) with no change in maximum response (Fig. 2). The signal transduction system for insulin action has not been completely established, but ST does not alter numbers or tyrosine-kinase activity for the insulin receptor [5]. The fact that ST-induced changes are downstream from these initial events in the signal transduction pathway is consistent with certain adipose tissue responses to insulin being altered (lipogenesis) whereas others are not (lipolysis).

The regulation of lipolysis involves cAMP and a signal transduction system that includes stimulatory G proteins (G_s) and inhibitory G proteins (G_i) (for reviews, see refs. [4,5]).

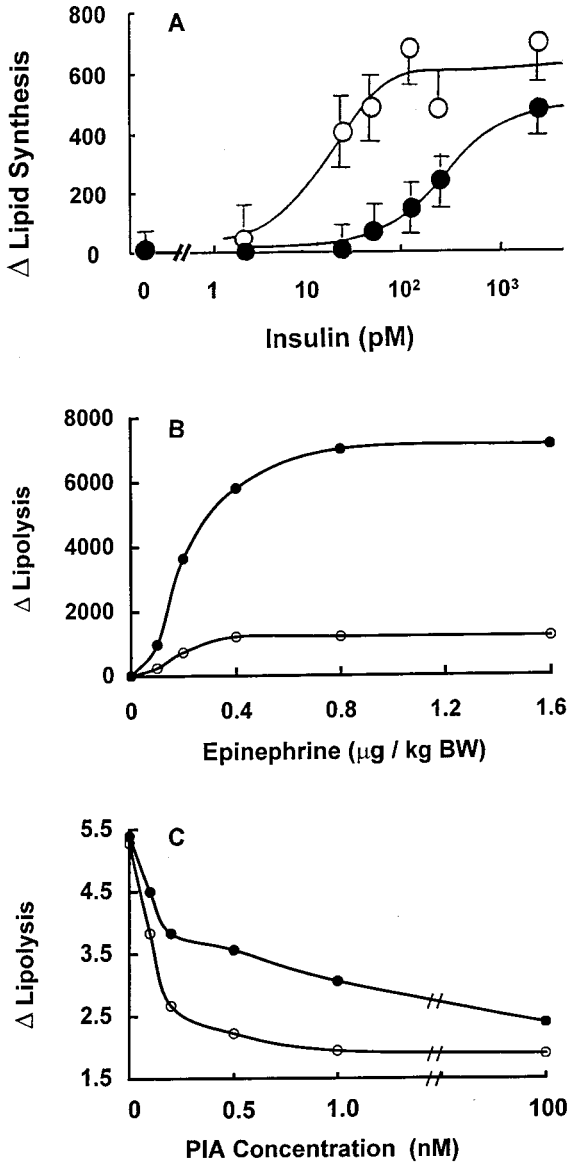

Fig. 2. ST effects on altering adipose tissue response to homeostatic signals. (*A)* Alterations in insulin stimulation of lipogenesis in control (open symbols) or pST-treated pigs (closed symbols). Rates represents glucose incorporation into lipids (nmol · 10^6 cells^{-1} · 2h^{-1}), and data are adapted from Walton and Etherton [37]. (B) Alterations in lipolysis in response to epinephrine challenge in control (open symbols) or bST-treated (closed symbols) lactating cows. Rates represent response in circulating NEFA (μMol · min^{-1} · L^{-1}), and data are adapted from Sechen et al. [38]. (*C*) Inhibition of lipolysis by adenosine analog phenylisopropyladenosine (PIA) in adipose tissue from control (open symbols) or bST-treated (closed symbols) lactating cows. Rates represent glycerol release (nmol · gm tissue^{-1} · 3h^{-1}), and data are adapted from Lanna et al. [39].

Catecholamines affect lipolysis through the G_s system, and ST treatment dramatically increased circulating NEFA when an epinephrine challenge was administered. In this case, the alteration involved an increase in maximum response (R_{max}) to catecholamines with no change in sensitivity (Fig. 2). Examination of the cellular site for these effects indicated that somatotropin treatment resulted in only modest changes in β- and α_2-adrenergic receptor numbers. Furthermore, G_s proteins and other downstream components of lipolytic signal transduction pathway did not differ in adipose tissue from bST-treated and control animals [4,5]. This suggested the major mechanism by which ST altered lipolysis may involve the antilipolytic system.

Adenosine is an autocrine/paracrine factor that exerts an acute antilipolytic effect via the G_i system. Chronic treatment with ST decreased the antilipolytic effects of adenosine in adipose tissue (for reviews, see refs. [4,5]). The diminution of adenosine's ability to inhibit lipolysis in ST-treated animals involved a substantial change in the sensitivity (ED_{50}) and a reduction in the R_{max} (Fig. 2). The mechanism did not involve changes in binding affinity or number of adenosine receptors, and the abundance of α, β, and γ subunits of the heterotrimeric G_i proteins that bind to the adenosine receptors was not altered. However, the functionality of the G_i proteins was reduced significantly with ST treatment [4,5]. Thus, a major mechanism by which ST alters lipolysis centers on the G-inhibitory system of adipose tissue, and the enhanced lipolytic response to catecholamines observed in vivo in ST-treated animals is in large part related to a relief in the tonic inhibition of lipolysis via changes in the G_i signaling cascade.

Overall, the changes in adipose tissue that occur with bST treatment allow for a chronic alteration of nutrient use. When a meal is consumed and circulatory insulin increases, the coordinated responses result in less nutrients being directed to body fat reserves because of the altered insulin sensitivity of adipose tissue, and more nutrients are taken up by the mammary gland consistent with the increased milk synthesis. Likewise, if nutrients are in inadequate supply, the coordinated responses require a greater mobilization of energy reserves to meet the needs associated with the increased milk synthesis, and this is accommodated by the greater lipolytic response to catecholamines. Overall, ST treatment alters the response to homeostatic signals effecting lipogenesis and lipolysis in an orchestrated manner to match the increased mammary gland use of nutrients for milk synthesis.

A second example of the mechanisms relates to the mammary gland. Knight and coworkers [40] demonstrated that ST treatment over a 22-week period prevented the decline in mammary cell numbers that normally occurs during lactation. Other studies with cows and goats have reported trends or significant increases in several key enzymes such as acetyl-CoA carboxylase, acetyl-CoA synthetase, and fatty acid synthase (for reviews, see refs. [4,5,35]). Thus, bST effects involve both an increase in the rates of milk synthesis per cell and an improved maintenance of secretory cells. Mechanisms by which ST affects mammary gland function are still uncertain but appear to be indirect involving the IGF system [6,29,41,42]. There are abundant type I and type II IGF receptors in bovine mammary tissue, but attempts to detect ST receptors in bovine mammary tissue have been unsuccessful, and only a very low level of expression of ST receptor message can be detected. As with nonlactating animals, the administration of exogenous bST increases circulating concentrations of IGF-I, IGFBP-3, and acid-labile subunit and decreases circulating IGFBP-2. Close-

arterial infusion of the mammary gland with bST had no effect on milk yield [43], whereas close-arterial infusion of IGF-I or IGF-II stimulates milk yield [44–46]. The lactational response to close-arterial infusion with IGFs is arguably the strongest evidence that this is the mechanism to explain bST effects on the mammary gland. Nevertheless, lactational responses to close-arterial infusion of IGFs are much less than obtained with systemic supply of bST. Thus, considerable work remains in establishing the mechanism of action whereby bST increases milk synthesis and secretion, and the specific roles for the IGFs, IGFBPs, and their proteases remain to be delineated.

2.5. Integration

There are several paradoxes concerning ST that need to be considered in developing an understanding of the mechanism of action (for review, see ref. [42]). One is that circulating ST is higher in genetically superior cows that have high milk yields; yet circulating ST is also elevated when cows are under adverse conditions such as chronic undernutrition or poor management, and in this case milk yields are low. A second paradox is the relationship between milk response to bST and quality of management, especially nutritional status. Furthermore, when bST is administered to cows fed inadequately or poorly managed, a negligible milk response occurs, but no adverse metabolic effects are observed. The relationship between ST and the IGF system appears to be key because the magnitude of changes in circulating IGF-I and some of the IGFBPs closely parallel the magnitude of the milk response that occurs with bST treatment [42].

Nutritional status plays a key role in the regulation of the ST/IGF system [47,48], and this provides the frame work to consider the variation in response to bST. A conceptual model is presented in Fig. 3. Administration of bST to well managed lactating cows causes an increase in circulating IGF-I and IGFBP-3 and a decrease in IGFBP-2. Thus, when nutritional status is excellent, bST has indirect effects on the mammary gland via the IGF system, and substantial increases in milk yield occur. In the case of a more moderate nutritional status, responses are attenuated with less dramatic changes in circulating IGF-I and IGFBPs and a smaller milk increase with bST treatment (Fig. 3). When nutritional status is severely compromised, the ability of bST to effect the IGF system is abolished and a negligible milk response occurs with bST treatment. Thus, in chronically underfed animals, direct effects on tissues such as adipose tissue and liver occur, but effects on the IGF system are uncoupled so that mammary use of nutrients is not stimulated (Fig. 3). This is discussed more extensively in several reviews [4,29,42,49], but it is clear that ST is an important homeorhetic control that functions across a wide range of physiological situations from high producing cows to animals that are poorly managed and have a low level of performance. Overall, the nutritional regulation of the ST/IGF system appears to be a particularly important component signaling the appropriate use of nutrients. These coordinated responses to nutrient supply ensure appropriate use of nutrients for productive functions so as to not compromise animal well being and health.

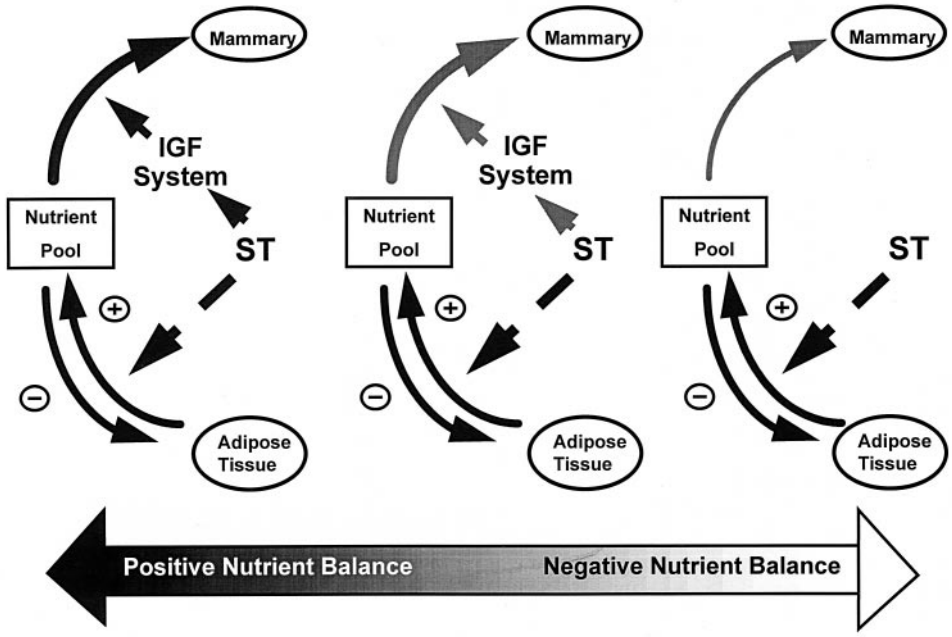

Fig. 3. Conceptual model illustrating effects of ST and nutritional modulation of the ST/IGF system. Direct effects of ST include alterations in activities of key enzymes and tissue response to homeostatic signals as represented by plus and minus symbols on adipose tissue rates of lipolysis and lipogenesis, respectively. Indirect effects involve effects of the IGFs and their binding proteins on mammary tissue, and these effects are modulated by nutritional status. Adapted from McGuire and Bauman [42].

3. Commercial application

3.1. Public perception

Public discussion of new technologies is an important component in the application of science, and this was especially true for bST as one of the first products of biotechnology. Prior to approval in the U.S., the National Institutes of Health conducted a Technology Assessment Conference and the Food and Drug Administration held a series of public hearings. In addition, safety evaluations were conducted by virtually every relevant medical/health association and scientific society. For example, the safety of food products was evaluated by the American Medical Association, American Academy of Pediatrics, American Cancer Society, Council on Agricultural Science and Technology, Food and Nutrition Science Alliance, Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). Without exception, all of the medical associations and scientific societies concluded that use of bST represented no health or safety concerns for consumers or cows [28,50].

There were individuals and special interest groups predicting dire consequences from bST use; their surveys and analysis indicated bST approval would cause a massive reduction in milk consumption, substantial decline in milk prices, and bankruptcy for many dairy farmers.

Examples of some of the more egregious claims were that use of bST would: cause cancer and an AIDS-like disease in consumers; increase the amount of pus and antibiotics in the milk and lower milk's quality and nutritive value; and result in mad cow disease, and a catastrophic increase in mastitis, hypermetabolic stress, and burnout in treated cows [51–53].

Media coverage of the bST debate was extensive with almost 800 reports (printed stories, broadcasts, and news wire releases) in the first quarter of 1994. During this interval, Gallup polls indicated that over 70% of the American public was aware of bST [54]. Nevertheless, consumer confidence remained high, and over the first year following bST approval, fluid milk consumption in the U.S. increased about 1% and milk prices to farmers increased by 2% [28,54]. To date, regulatory agencies in more than 50 countries have completed safety evaluations and approved bST, although several of these countries have a political moratorium on its use [28,50]. Recently, a joint commission of the FAO/WHO re-evaluated the safety issues and again concluded that commercial use of bST represents no safety concerns [55].

U.S. food laws do not mandate labeling of milk from bST-treated cows because treatment has no effect on nutrient composition [6]. However, laws do allow the development of a niche market where milk could be labeled as coming from cows that did not receive recombinant bST. Under U.S. labeling laws, this claim has to be truthful; given that there is no test to validate lack of use, a certificate signed by the producer was accepted as adequate verification that bST was not being used. Many grocery stores carry the "recombinant bST-free" milk; in upstate New York, use peaked at about 2% of total fluid milk sales shortly after bST approval, and currently represent less than 1% of total sales.

3.2. Commercial use in the United States

The Center of Veterinary Medicine of the Food and Drug Administration approved Monsanto's prolonged release formulation of bST, and commercial sales began in February 1994 under the trade name of Posilac. Use has gradually increased to where ≈3 million cows are currently receiving bST. Use involves herds of all sizes representing all geographic regions [28], and through 1998 Monsanto has sold over 100 million doses of their 2-week formulation (R. Collier, Monsanto Co., personal communication). Anecdotal information from extension personnel indicates field performance has borne out results from the scientific studies. No special diets have been required, and user herds range from pasture-based operations to those feeding total mixed diets. However, quality of management is clearly the major factor influencing response to bST, and allowing an adequate intake of a balanced diet represents a major component in the quality of management [6,25,28]. Response has been observed for cows of varying genetic merit. In fact, some herds using bST have an annual milk yield of over 15,000 kg/cow, and individual treated cows have produced over 27,000 kg/year.

We recently examined the commercial impact of bST on dairy farms in the Northeastern U.S. [56]. Using Dairy Herd Improvement milk test data and Monsanto sales records, we identified two groups of herds—a control group that never purchased bST and a group that had used bST continuously following approval on at least 50% of their cows. We analyzed an 8-year period—4 years preapproval and the 4 years postapproval. The data set represented

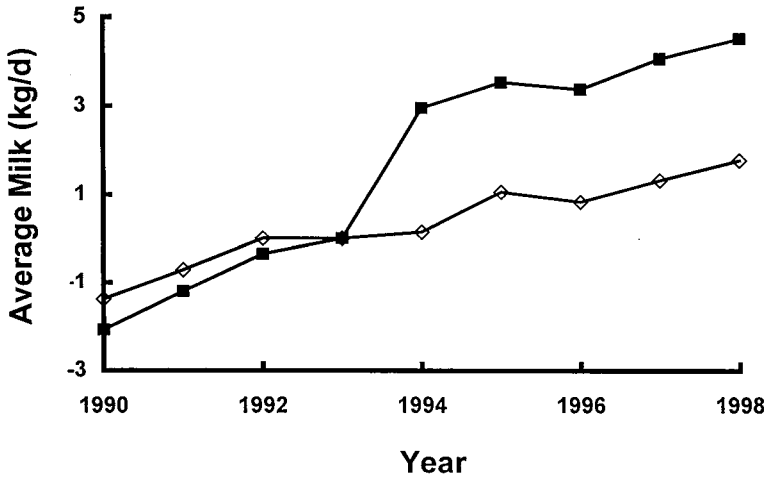

Fig. 4. Milk responses to bST in the Northeast dairy herds. Use of bST commenced in February 1994, and data encompass a preapproval period (January 1990 through 1993) and a postapproval period (July 1994 through March 1998). Control herds (open diamond) never purchased bST, and bST herds (closed squares) used bST continuously throughout the postapproval period. Data represent 340 herds and over 80,000 cows and 200,000 lactations; for comparison, daily yields are expressed relative to 1993, the year before bST approval. Adapted from Bauman et al. [56].

340 herds and involved over 80,000 cows and 200,000 lactations [56]. Comparisons demonstrated that bST herds were the same as control herds except they had increased yields of milk, milk fat, and milk protein. Over the postapproval period, daily milk yield was increased to a similar extent each year and averaged about 3 kg across all milking cows on each test day (Fig. 4). However, some cows are ineligible to receive bST treatment (<60 days postpartum), and only a portion of eligible cows are being treated. Assuming producers are treating ≈75% of eligible cows, the observed milk response would average almost 5 kg/day over the last two-thirds of the lactation cycle.

Commercial use of bST also has introduced some new paradigms in dairy production. For example, producers that are constrained by animal waste and environmental regulations have been able to use bST to increase milk yield and net farm income. Treatment with bST results in less animal waste (fecal and urine) per unit of milk produced [6,57]. Another new paradigm relates to the increased persistency in milk yield. A 12-month calving interval generally has been considered most economical, but the increased persistency with bST treatment shifts the economics to favor extended lactations. Progressive producers are currently experimenting to determine the optimum calving interval, and it appears to be substantially greater for first parity heifers as compared with multiparous cows [58]. This shift has a dramatic impact on many aspects of the dairy herd because most health problems and stress occur during the interval around parturition. On a herd basis, extended lactation results in fewer parturitions, lower incidence of postpartum metabolic diseases, lower veterinary costs, and an overall improvement in herd life, animal well being, and dairy farm profitability [58,59].

References

[1] Evans HM, Simpson ME. Hormones of the anterior hypohysis. Am J Physiol 1931;98:511–46.
[2] Stricker P, Grueter F. Action du lobe antérieur de l'hypophyse sur la montée laiteuse. Comptes Rendus 1928;99:1778–980.
[3] Asdell SA. The effect of the injection of hypophyseal extract in advanced lactation. Am J Physiol 1932;100:137–40.
[4] Bauman DE, Vernon, RG. Effects of exogenous bovine somatotropin on lactation. Ann Rev Nutr 1993; 13:437–61.
[5] Etherton TD, Bauman DE. The biology of somatotropin in growth and lactation of domestic animals. Physiol Rev 1998;78:745–61.
[6] Bauman DE. Bovine somatotropin: review of an emerging animal technology. J Dairy Sci 1992;75:3432–51.
[7] Asimov GJ, Krouze NK. The lactogenic preparations from the anterior pituitary and the increase in milk yield from cows. J Dairy Sci 1937;20:289–306.
[8] Folley SJ, Young FG. The effect of anterior pituitary extracts on established lactation in the cow. Proc R Soc Lond B 1938;126:45–76.
[9] Young FG. Experimental stimulation (galactopoiesis) of lactation. Br Med Bull 1947;5:155–60.
[10] Hammond J. Physiological limits to intensive production in animals. Br Agric Bull 1952;4:222–4.
[11] Young FG. IV. Growth hormone and metabolism; the growth hormone and diabetes. Rec Prog Horm Res 1953;8:471–97.
[12] Hutton JB. The effect of growth hormone on the yield and composition of cows milk. J Endocrinol 1957;16:115–25.
[13] Williams WF, Lee SD, Head HH, Lynch J. Growth hormone effects on bovine plasma fatty acid concentration and metabolism. J Dairy Sci 1963;46:1405–8.
[14] Cotes PM, Reid M, Young FG. Diabetogenic action of pure anterior pituitary growth hormone. Nature 1949;64:209–11.
[15] Machlin L. Effect of growth hormone on milk production and feed utilization in dairy cows. J Dairy Sci 1973;56:575–80.
[16] Brumby PJ, Hancock J. The galactopoetic role of growth hormone in dairy cattle. N Z J Sci Technol 1955;36:417–36.
[17] Kronfeld DS. Growth hormone induced ketosis in the cow. J Dairy Sci 1965;48:342–6.
[18] Kronfeld DS. Major metabolic determinants of milk volume, mammary efficiency and spontaneous ketosis in dairy cows. J Dairy Sci 1982;65:2204–12.
[19] Bauman DE, Currie, WB. Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis. J Dairy Sci 1980;63:1514–29.
[20] Bauman DE, McCutcheon SN, Steinhour WD, Eppard PJ, Sechen SJ. Sources of variation and prospects for improvement of productive efficiency in the dairy cows: a review. J Anim Sci 1985;60:583–92.
[21] Bines JA, Hart IC. Metabolic limits to milk production, especially roles of growth hormone and insulin. J Dairy Sci 1982;65:1375–89.
[22] Hart IC. Endocrine control of nutrient partition in lactating ruminants. Proc Nutr Soc 1983;42:181–94.
[23] Bauman DE, DeGeeter MJ, Peel CJ, Lanza GM, Gorewit RC, Hammond RW. Effect of recombinantly derived bovine growth hormone (bGH) on lactational performance of high yielding dairy cows. J Dairy Sci 1982;65(suppl 1):121.
[24] Bauman DE, Eppard PJ, DeGeeter MJ, Lanza GM. Responses of high-producing dairy cows to long-term treatment with pituitary somatotropin and recombinant somatotropin. J Dairy Sci 1985;68:1352–62.
[25] Crooker BA, Otterby DE. Management of the dairy herd treated with bovine somatotropin. Vet Clin North Am Food Anim Pract 1991;7:417–36.
[26] Burton JL, McBride BW, Block E, Glimm DR, Kennelly JJ. A review of bovine growth hormone. Can J Anim Sci 1994;74:167–201.
[27] National Research Council. Metabolic modifiers: effects on the nutrient requirements of food-producing animals. Washington, DC: National Academy Press, 1994.

[28] Hartnell GF. Bovine somatotropin: production, management and United States experience. In: Ivan M, editor. Animal science research and development: moving toward a new century. Ottawa, Canada: Center for Food and Animal Research, Agriculture and Agri-Food, 1995. p. 189–203.
[29] Chilliard Y, Colleau J-J, Disenhaus C, Lerondelle C, Mouchet C, Paris A. L'hormone de croissance recombinate: intérêt et risques potentiels de son utilisation pour la production laitière bovine. INRA Prod Anim 1998;11:15–32.
[30] Tyrrell HF, Brown ACG, Reynolds PJ, Haaland GL, Bauman DE, Peel CJ, Steinhour WD. Effect of bovine somatotropin on metabolism of lactating dairy cows: energy and nitrogen utilization as determined by respiration calorimetry. J Nutr 1988;118:1024–30.
[31] Kirchgessner M, Windisch W, Schwab W, Muller HL. Energy metabolism of lactating dairy cows treated with prolonged-release bovine somatotropin or energy deficiency. J Dairy Sci 1991;74(suppl 2):35–43.
[32] Laurent F, Vignon B, Coomans D, Wilkinson J, Bonnel A. Influence of bovine somatotropin on the composition and manufacturing properties of milk. J Dairy Sci 1992;75:2226–34.
[33] Van den Berg GA. A review of quality and processing suitability of milk from cows treated with bovine somatotropin. J Dairy Sci 1991;74(suppl 2):2–11.
[34] Peel CJ, Bauman DE. Somatotropin and lactation. J Dairy Sci 1987;70:474–86.
[35] Baldwin RL, Knapp JR. Recombinant bovine somatotropins effects on patterns of nutrient utilization in lactating dairy cows. Am J Clin Nutr 1993;58(suppl):282S-6S.
[36] Vernon RG, Flint DJ. Role of growth hormone in the regulation of adipocyte growth and function. In: Heap RB, Prosser CJ, Lamming GE, editors. Biotechnology in growth regulation. London: Butterworth, 1989. p. 57–71.
[37] Walton PE, Etherton TD. Stimulation of lipogenesis by insulin in swine adipose tissue: antagonism by porcine growth hormone. J Anim Sci 1986;62:1584–95.
[38] Sechen SJ, Dunshea FR, Bauman DE. Somatotropin in lactating cows: effect on response to epinephrine and insulin. Am J Physiol 1990;258:E582–8.
[39] Lanna DPD, Houseknecht KL, Harris, DM, Bauman DE. Effect of somatotropin treatment on lipogenesis, lipolysis and related cellular mechanisms in adipose tissue of lactating cows. J Dairy Sci 1995;78:1703–12.
[40] Knight CH, Fowler PA, Wilde CJ. Galactopoietic and mammogenic effects of long-term treatment with bovine growth hormone and thrice daily milking in goats. J Endocrinol 1990;127:129–38.
[41] Cohick WS. Role of insulin-like growth factors and their binding proteins in lactation. J Dairy Sci 1998;81:1769–77.
[42] McGuire MA, Bauman DE. Regulation of nutrient use by bovine somatotropin: the key to animal performance and well-being. In: Martens H, editor. Berlin: Proc IXth Inter Conf Prod Diseases Farm Anim,. Free University of Berlin, Fac Vet Med, 1997. p. 125–137.
[43] McDowell GH, Hart IC, Kriby AC. Local intra-arterial infusion of growth hormone into the mammary glands of sheep and goats: effects on milk yield and composition, plasma hormones and metabolites. Aust J Biol Sci 1987;40:181–9.
[44] Prosser CG, Fleet IR, Corps AN, Froesch ER, Heap RB. Increase in milk secretion and mammary blood flow by intra-arterial infusion of insulin-like growth factor-I into the mammary gland of the goat. J Endocrinol 1990;126:437–43.
[45] Prosser CG, Davis SR. Milking frequency alters the milk yield and mammary blood flow response to intra-mammary infusion of insulin-like growth factor-I in the goat. J Endocrinol 1992;135:311–6.
[46] Prosser CG, Davis SR, Farr VC, Moore LG, Gluckman PD. Effects of close-arterial (external pudic) infusion of insulin-like growth factor-II on milk yield and mammary blood flow in lactating goats. J Endocrinol 1994;142:93–9.
[47] McGuire MA, Vicini JL, Bauman DE, Veenhuizen JJ. Insulin-like growth factors and binding proteins in ruminants and their nutritional regulation. J Anim Sci 1992;70:2901–10.
[48] Breier GH. Regulation of protein and energy metabolism by the somatotropic axis. Domest Anim Endocrinol 1999;17:209–18.
[49] Flint DJ, Vernon RG. Effects of food restriction on the responses of the mammary gland and adipose tissue to prolactin and growth hormone in the rats. J Endocrinol 1998;156:299–305.

[50] Bauman DE, McBride BW, Burton JL, Sejrsen K. Somatotropin (bST). Brussels, Belgium: International Dairy Federation Technical Report. International Dairy Federation, Bulletin 1994. Vol. 293, pp. 2–7.
[51] Kronfeld DS. Recombinant bovine growth hormone: cow responses delay drug approval and impact public health. In: Liebhard WC, editor. The dairy debate. Davis, CA: University California, Sustainable Agriculture Research and Education Program, 1993. p. 65–112.
[52] Hansen M, Halloran JM, Groth E III, Leferts LY. Potential public health impacts of the use of recombinant bovine somatotropin in dairy production. Rome, Italy: Report of the Fiftieth Meeting of FAO/WHO Expert Committee on Food Additives, 1998. p. 17–26.
[53] Epstein SS. Potential public health hazards of biosynthetic milk hormones. Int J Health Serv 1990;20:73–84.
[54] National Milk Producers Federation. Dairy Industry Collation Press Release. Washington, DC: Dairy Industry Collation, February 1995.
[55] FAO/WHO. Recombinant bovine somatotropin (addendum). In: WHO Food Additives Series 41, Toxicological Evaluation of Certain Veterinary Drug Residues in Food (Report of the Fiftieth Meeting of FAO/WHO Expert Committee on Food Additives (JECFA)). Geneva, Switzerland: World Health Organization, 1998. p. 125–46.
[56] Bauman DE, Everett RW, Weiland W, Collier RJ. Production responses to bovine somatotropin in northeast dairy herds. J Dairy Sci 1999;82: in press.
[57] Johnson DE, Ward GM, Torrent J. The environmental impact of bovine somatotropin use in dairy cattle. J Environ Qual 1992;21:157–62.
[58] Van Amburgh ME, Galton DM, Bauman DE, Everett RW. Management and economics of extended calving intervals with use of bovine somatotropin. Livest Prod Sci 1997;50:15–28.
[59] Knight C. Extended lactation. In: Hannah Research Institute Yearbook. Ayr, Scotland: Hannah Research Institute, 1998. p. 30–9.