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Biology of Somatotropin in Growth and Lactation of Domestic Animals

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Etherton, Terry D., and Dale E. Bauman. Biology of Somatotropin in Growth and Lactation of Domestic Animals. *Physiol. Rev.* 78: 745–761, 1998.—Impressive progress has been made during the past 15 years in our understanding of the biology of somatotropin (ST) in domestic animals. In part, this progress was sparked by advances in biotechnology that made feasible the production of large quantities of recombinant bovine ST (bST) and porcine ST (pST). The availability of recombinant bST and pST resulted in an exponential increase in investigations that explored their role in growth and lactation biology, as well as evaluated their potential for commercial use. Collectively, these studies established that administration of bST to lactating dairy cows increased milk yield, and treatment of growing pigs with pST markedly stimulated muscle growth and reduced fat deposition. In addition to these "efficacy" studies, a substantial number of investigations examined the mechanisms by which ST affects lactation and growth of domestic animals. This review summarizes the diverse physiological effects ST has on growth and lactation and discusses the underlying mechanisms that mediate these effects in domestic animals.

I. INTRODUCTION

Technological developments in a variety of scientific and engineering disciplines will be needed to support the growing world population, which is expected to double in the next 40 years. It has been estimated that the supply of food required to adequately meet human nutritional needs over the next 40 years is quantitatively equal to the amount of food previously produced throughout the history of humankind (137). To meet this need, it will be essential that scientists continue to develop new technologies that increase productive efficiency of food production. With respect to animal agriculture, administration of exogenous somatotropin (ST) is one biotechnology that increases the food output (meat or milk) per unit of feed resource input. In addition to positive effects on the efficiency of food production, the benefits of ST include effects on environmental impact through reductions in animal waste products and expenditures for feed production, including fertilizer and other inputs associated with growing, harvesting, processing, and storing animal feed (13, 101).

Another important impetus for developing biotechnologies for animal agriculture is the need to reduce the fat content of fresh meat products. Numerous studies have shown that ST effectively alters nutrient use in growing animals in a manner that markedly reduces the amount of carcass fat. This is important because of the evidence that certain saturated fatty acids (e.g., myristic and palmitic acids) found in animal fat potently elevate low-density lipoprotein cholesterol levels, a major risk factor for coronary heart disease (4, 113). Because animal products provide ~60–70% of the total saturated fatty acids in the

average American diet (103), it is evident that new technologies that reduce fat content of fresh meat will be of benefit to consumers who wish to reduce their risk of chronic diseases.

Somatotropin was first characterized in the 1920s when Evans and Simpson (72) demonstrated growth-promoting effects in rats treated with a crude extract from bovine pituitaries. The discovery that the pituitary contained a factor that stimulated growth led to this factor being referred to as "growth hormone." It became apparent shortly thereafter, however, that growth hormone did much more than stimulate growth, since administration of pituitary extracts also enhanced milk yield in lactating rats (166) and goats (6) and reduced carcass fat in growing rats (22, 55, 117). Another major development in ST research occurred in 1937 when Russian scientists treated 600 dairy cows and demonstrated that milk yield was increased as long as administration of pituitary extract continued (7). It was not until 1945, however, that ST was isolated from the anterior pituitary (119). This allowed Li et al. (120) to conduct the first experiment to show that crude preparations of ST mimicked the effects the alkaline pituitary extract had on carcass fat in rats. Others extended this finding to lactation and demonstrated that ST was the galactopoietic factor in pituitary extracts (188). In addition, British scientists conducted studies in the 1940s to evaluate the potential of using bovine ST (bST) to help alleviate food shortages during World War II. Although they found bST increased the milk yield of dairy cows, the amount of bST that could be extracted from the pituitary glands of slaughtered animals was inadequate to impact commercial production (188).

Breakthroughs in biotechnology in the early 1980s enabled ST to be produced by recombinant DNA technology. This resulted in the first study in 1982 in which recombinantly derived ST was administered to domestic animals. In this study, lactating cows were treated with recombinant bST (14). The subsequent production of large quantities of recombinant bST and porcine ST (pST) resulted in an exponential increase in investigations that explored the role of ST in growth and lactation biology, as well as evaluated their potential for commercial use. Collectively, these studies resulted in an unprecedented increase in our understanding of how ST affects growth and lactation of domestic animals. Thus the objectives of this review are *1*) to provide an overview of the remarkable biological effects that ST has on lactation and growth of domestic animals and *2*) to review our present understanding of the biological mechanisms that account for the diverse and orchestrated effects ST has on metabolism and nutrient partitioning. The focus of this review is on growing pigs and lactating dairy cows because the database related to production responses and the biological mechanisms of ST action is much more extensive for these species than for other domestic animals.

II. STRUCTURE OF SOMATOTROPIN

Somatotropin is a protein hormone synthesized in and secreted from the anterior pituitary gland. Somatotropin secretion is regulated by two well-characterized hypothalamic peptides that act to stimulate (growth hormone-releasing factor; GRF) or inhibit (somatostatin) release of ST from the pituitary gland (169). In addition to these two peptides, evidence (reviewed in Ref. 162) indicates that a third as yet unidentified hormone binds to the growth hormone secretagogue receptor to stimulate ST release using a signal transduction pathway distinct from that of GRF. Somatotropin contains 191 amino acids, and bST and pST share a high degree of amino acid sequence similarity (~90%; Refs. 19, 68). In contrast, the amino acid sequence of both bST and pST is appreciably different from human ST (hST) (~35% of the amino acids in hST differ from both bST and pST). Because of this difference, bST and pST have no effect on human growth, consistent with their binding affinity to the hST receptor being several orders of magnitude lower than that of hST (36, 118, 135).

It is important to appreciate that there are variant forms of ST. For example, bST is released from the pituitary as four variants. These variants have either a leucine or valine substitution at position 127 and an alanine (191-amino acid sequence) or a phenylalanine (190-amino acid sequence) at the NH_2 terminus (185). The variation in the NH_2 terminus is due to differences in cleavage of the signal peptide. The frequency of these gene alleles differs between dairy breeds (122). Furthermore, there is some indication that these variants may differ in their potency. Although studies have been limited, results indicate that treatment with the valine-127 variant elicited a greater increase in circulating ST and milk yield than the leucine-127 variant (63, 64). The commercial bST formulation (Monsanto, St. Louis, MO) approved for use in dairy cows is the 190-amino acid variant with leucine at position 127, and it has an extra methionine at the NH_2 terminus.

The three-dimensional structure of pST (1) and hST (50, 182, 183) has been established. Somatotropin consists of four α-helices and adjoining regions of nonhelical polypeptide. Each ST molecule is bivalent because it contains two separate sites (site 1 and site 2) that bind to different ST receptors. Indeed, bST has been shown to bind to recombinant ST binding protein (the extracellular domain of the receptor) in a 1:2 molar ratio, suggesting that bST forms a homodimer with its receptor (165). Although we are unaware of any similar data regarding pST receptor dimerization, it seems likely that this occurs because of the structural similarities between hST, bST, and pST and their respective receptors. Dimerization of the ST receptors occurs in a sequential manner, with site 1 interacting with a receptor followed by site 2 binding. Studies with

transgenic mice expressing bST mutated in site 2 also have shown that these mice do not have the characteristic growth response (38).

The ST receptor for cattle and pigs has been cloned (41, 92). The pST receptor cDNA sequence shares 89% sequence identity with the hST receptor cDNA (41), and the bST receptor cDNA sequence is 76% identical (92). Thus the sequence similarities among the pST, bST, and hST receptors are much greater than for the respective hormones that bind to the homologous receptor. A number of mRNA variants for the ST receptor have been reported for cattle (93), sheep (142), and other species including humans (189). Studies have shown that a single arginine residue in the hST receptor is the major determinant of species specificity in ST binding (164).

III. EFFICACY OF SOMATOTROPIN

A. Growth

Somatotropin has been shown to have impressive effects on nutrient partitioning between muscle and adipose tissue that leads to a dramatic alteration in the growth of these tissues. Daily administration of maximally effective doses of pST ($\geq$100 $\mu g \cdot kg$ body $wt^{-1} \cdot day^{-1}$) to growing pigs for 30–77 days can increase average daily gain ~10–20%, improve feed efficiency (i.e., the ratio of feed consumed to body weight gain) 13–33%, decrease lipid accretion rates by as much as 70%, and stimulate protein deposition (muscle growth) by as much as 62% (reviewed in Refs. 66, 68, 137). In general, responses in lean tissue accretion to ST treatment have been less for growing ruminants than observed for pigs. However, this species difference appears to relate to the difficulty in ensuring an amino acid supply that is adequate in balance and quantity. When the supply of rumen microbial protein is complemented with additional amino acids that escape rumen fermentation, the dramatic increase in protein accretion with bST treatment of ruminants is comparable to that observed with pST treatment of growing pigs (reviewed in Refs. 27, 137).

It is evident that pST administration has dramatic effects on protein accretion even in pigs highly selected for rapid growth and high rates of protein accretion (34). This is vividly illustrated by the results in Table 1, which show the effects of pST on rate of protein accretion in pigs that are considered to be "genetically elite" for rapid protein accretion. In this study, boars (intact males) treated with pST gained 273 g protein/day. This is the highest rate of protein deposition observed in pigs to date and corresponds to a muscle growth rate of ~1.4 kg/day. When this rate of protein accretion rate is compared with that observed for elite pigs not treated with pST (162 g/day), it is apparent that the biological capacity or "ceiling" (as estimated by maximally effective doses of pST) for protein accretion is still considerably greater than rates presently attained despite the impressive improvements that have occurred with genetic selection over the last several decades in protein accretion rate. This suggests that considerable progress in increasing protein accretion rate can still be made with genetic selection programs that use protein accretion rate as a selection criterion.

TABLE 1. *Effect of pST on accretion rates of protein and lipid in growing pigs (60–90 kg)*

		Accretion Rate, g/day	
Gender	pST, μg/kg	Protein	Lipid
Male	0	162	340
	100	273	134
Female	0	119	344
	100	220	134

Dose of porcine somatotropin (pST) represents daily dose. Adapted from Campbell et al. (34).

The early studies evaluating the effects of pST on growth and carcass composition (40, 71, 73) suggested that responsiveness was age dependent. This has been verified in subsequent studies (Table 2) that have shown the increase in growth rate and effects on protein and lipid deposition with pST treatment are significantly greater in the latter phase of the growth cycle. The mechanisms that account for this remain unclear.

There is a good understanding of how changes in the pST dose affect various parameters of growth, productive efficiency, and carcass composition (28, 73, 137). Collectively, these studies have established that the dose relationship varies considerably among the different parameters (see Fig. 1). For example, body weight growth and rate of protein accretion are maximally stimulated at a daily dose of pST of ~100 μg/kg body wt. In contrast, lipid accretion rate and the ratio of feed consumed to body weight decrease in a more linear manner over a range of pST up to 200 μg/kg body wt (see Fig. 1). The fact that there are differences in the shape of the dose-response curves is important because it illustrates that pST affects growth and nutrient metabolism of adipose tissue and muscle by different mechanisms. This is further illustrated by how dietary protein restriction affects lipid and protein accretion in pST-supplemented pigs (Fig. 2). The stimulatory effects of pST on protein accretion and circulating insulin-like growth factor (IGF)-I are progressively decreased until they are completely blunted as dietary protein levels decline (Fig. 2). In contrast, the ability of pST to reduce lipid accretion occurs across the range of dietary protein, even with the diets that contain the

TABLE 2. *Summary of levels of performance and accretion rates of protein and lipid and responses to exogenous pST across different phases of growth in pigs*

Phase of Growth	pST, μg/kg	Gain, g/day	Gain/Feed	Accretion Rate, g/day	
				Protein	Lipid
10–25 kg*	0	680	0.61	96	89
	120	680 (0)	0.61 (0)	113 (+17)	61 (−31)
20–50 kg†	0	900	0.43	120	207
	150	990 (+10)	0.49 (+13)	150 (+25)	122 (−41)
50–100 kg†	0	1,140	0.33	135	340
	150	1,334 (+17)	0.44 (+33)	235 (+74)	61 (−82)

Dose of pST represents daily dose. Values in parentheses are response to pST treatment (in %). [* Data from Harrell et al. (89). † Data from Boyd et al. (27).]

lowest protein levels. Collectively, the results depicted in Figs. 1 and 2 also provide valuable insight about nutrient requirements of pigs treated with pST. The marked changes that occur in compositional growth and growth rate in pigs treated with pST clearly underscore the importance of making adjustments in the dietary amino acid-calorie relationship to ensure an adequate availability of essential amino acids to accommodate the enhanced rate of protein accretion. This is particularly important because this dose of pST decreases feed intake.

The precipitous decrease in lipid deposition (see Fig. 1) observed when pigs are treated with a daily dose of 30–200 μg pST/kg body wt illustrates the magnitude to which pST can alter nutrient utilization by adipose tissue and subsequent adipocyte hypertrophy. The effect of pST to decrease glucose (the primary substrate for lipogenesis in pig adipose tissue) utilization in adipose tissue results in a situation where glucose that is normally used for lipogenesis is redirected to other tissues, primarily muscle. This metabolic adaptation is important because it *1*) decreases the rate of adipocyte hypertrophy and, hence, the rate of adipose tissue accretion and *2*) accounts for the effects that ST has on productive efficiency as well as contributes to the increase in muscle growth.

B. Lactation

Administration of exogenous ST has been shown to enhance lactational performance in mammals ranging

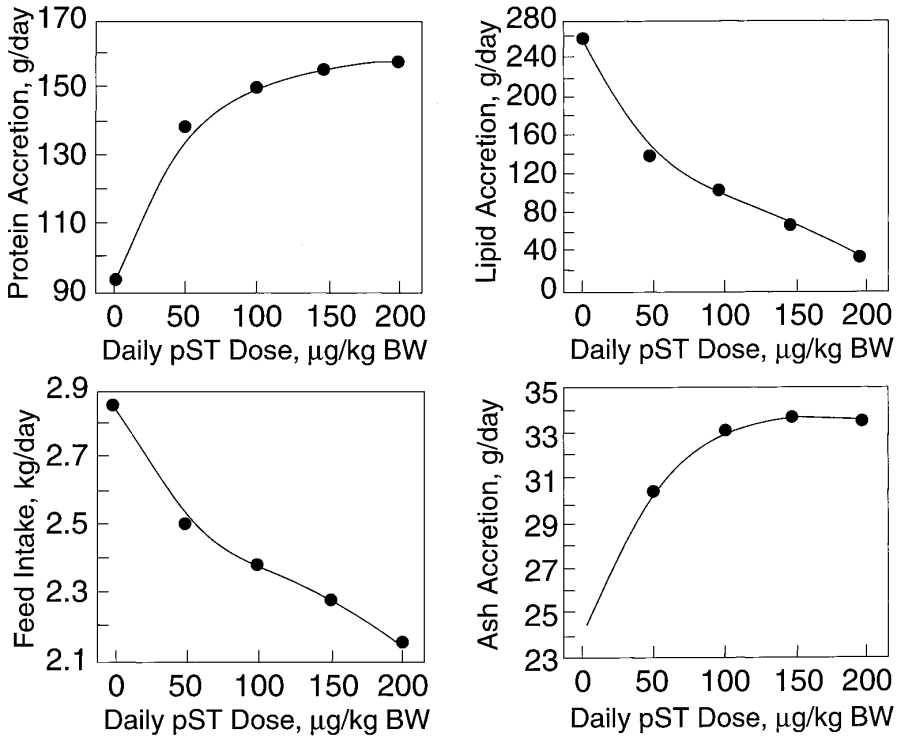

FIG. 1. Relationship between porcine somatotropin (pST) dose and different parameters of growth performance (68). BW, body weight. [Adapted from Boyd and Bauman (26) and Boyd et al. (27).]

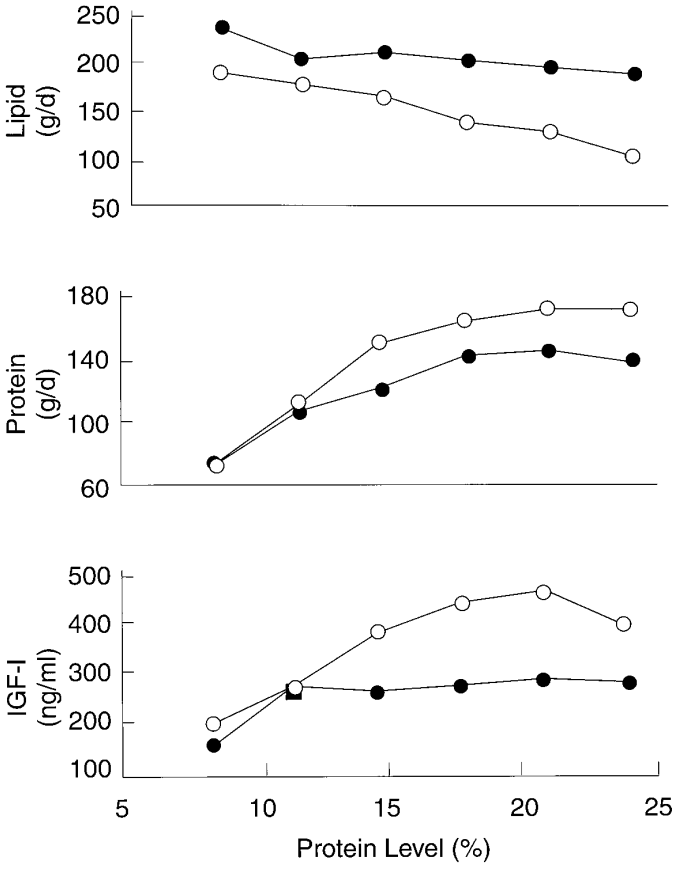

FIG. 2. Effect of dietary protein level on circulating insulin-like growth factor (IGF)-I and rates of lipid and protein accretion in growing pigs treated with pST (90 μg/day from 30 to 60 kg body wt; ○) or excipient (●). Dietary protein levels were 8.9, 11.4, 14.5, 17.6, 20.7, and 23.8%. [Constructed using data of Campbell et al. (33).]

from laboratory animals to humans (19, 85, 134). In the case of farm animals, a milk yield response has been demonstrated with ST treatment of pigs, sheep, goats, and cows. The majority of research has involved dairy cows, and bST has been approved for commercial use in 25 countries. Additional countries have approved but have a political moritorium on its use, e.g., European Union (91). Commercial use in the United States commenced in early 1994, and adoption was unusually rapid for an agricultural technology; ~2 million dairy cows were receiving bST by 3 years postapproval.

Milk yield response to bST has been observed for all dairy breeds and in animals of different parity and genetic potential (30, 91, 137). In general, response is negligible in early lactation before peak yield, so bST use is over the last 80% of the lactation cycle. Typical milk yield responses are increases of 10–15% (~4–6 kg/day), although even greater increases occur when the management and care of the animals are excellent (13, 39, 137). The pattern of response is one where milk yield gradually increases over the first few days of bST treatment and reaches a maximum during the first week. If treatment is terminated, milk yield gradually returns to pretreatment levels over a similar time period. However, when treatment is continued, the increased milk yield is maintained (Fig. 3). Thus bST results in a greater peak milk yield and an increased persistency in yield over the lactation cycle. As a consequence of the changes in the lactation curve, commercial use of bST has allowed a shift to extended lactations. On a herd basis, this 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 (171).

Lactational response to bST is a function of the daily dose represented by a hyperbolic dose-response curve with a pattern of diminishing marginal returns to increasing doses (17, 129). The daily bST dose needed to optimize milk yield response results in blood concentrations of ST that are within the range typically observed during episodic release of endogenous hormone, but average daily concentrations are severalfold higher than before treatment. Milk yield response appears to be related to the average daily ST concentration rather than a particular

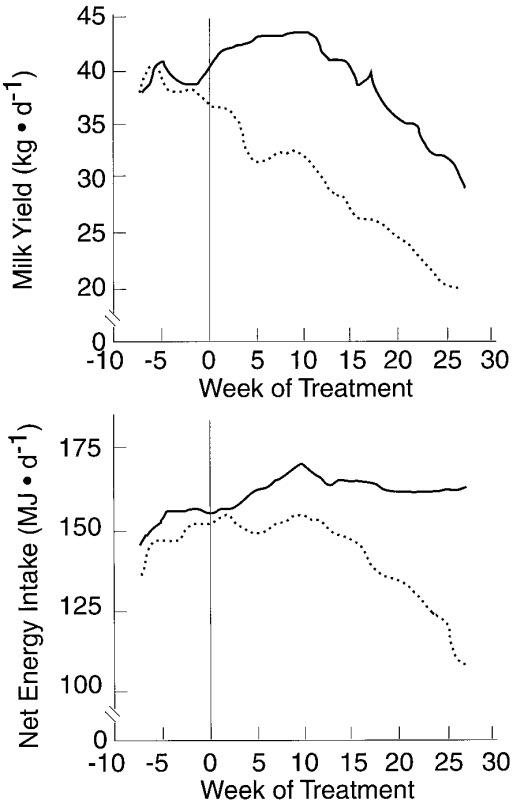

FIG. 3. Effect of bovine somatotropin (bST) on milk yield and voluntary intake. Commencing at *week 0* (84 ± 10 days postpartum), cows received a daily injection of excipient (dotted line) or bST (27 mg/day; solid line) for 26 wk. [Adapted from Bauman et al. (16).]

pattern of circulating ST. Studies have demonstrated a similar milk yield increase regardless of whether the daily dose of bST was administered as a single bolus, constant infusion, or as equal episodic pulses at 4-h intervals (17). The commercial form of bST presently used in the United States is a prolonged-release formulation (500 mg methionyl-bST; Monsanto) that is administered every 2 wk (91). The formulations of other companies are currently being evaluated by the Food and Drug Administration.

The gross composition of milk (fat, protein, and lactose) is not altered by treatment with bST (9, 13, 30, 37, 172). Thus the daily output of the major milk constituents is increased by an amount comparable to the increase in milk volume. The concentrations of fat and protein in milk normally vary as a result of factors such as genetics, breed, stage of lactation, season, diet, and nutritional status. These same factors also affect the composition of milk from bST-treated cows. In addition, proportions of total milk protein, represented by whey proteins and the different casein fractions, and the fatty acid composition are not substantially altered. As a result, use of bST has no impact on manufacturing characteristics of milk (9, 116, 172, 190).

Microconstituents of milk are also unchanged. For example, milk from bST-treated cows does not differ in vitamin content or in concentrations of nutritionally important mineral elements (13, 172). Milk also contains many hormones and growth factors; two that have received substantial attention are ST and IGF-I. At the bST doses that enhance milk yield, the concentration of bST in milk is unchanged. In fact, the milk concentration of bST is only increased when provocative doses of exogenous bST are administered to dairy cows (30, 104). In the case of IGF-I, small increases in milk concentrations were observed in the initial studies. As the number of animals and range of situations were expanded, it became evident that milk IGF-I varied widely between cows and was affected by many factors (e.g., herd, stage of lactation, environment), and use of bST has minimal, if any, impact on the milk concentration of IGF-I (44, 46, 75, 104). Overall, studies of the macro- and microcomponents of milk indicate that composition is unaltered by use of bST.

The major factor affecting the magnitude of milk response to bST is the quality of management (13, 45, 130, 145). Of special importance is the nutritional program. Milk production responses to bST are not dependent on special diets or unique feed ingredients, but animals must receive adequate amounts of a balanced diet. Overall, daily nutrient requirements are increased by an amount equal to the increase in milk, and productive efficiency (milk per unit of feed) is improved because a greater proportion of the nutrient intake is used for milk synthesis (13, 137). In fact, the gain in productive efficiency obtained with bST use would take 10–20 years to achieve using a combination of artificial insemination (semen from superior sires) and embryo transfer (13).

IV. MECHANISMS OF SOMATOTROPIN ACTION

The range of biological effects ST has on growth and lactation is extraordinary (Table 3). Somatotropin orchestrates many diverse physiological processes so that more nutrients can be used for lean tissue accretion (during growth) or milk synthesis (during lactation). Somatotropin is a homeorhetic control that affects numerous target tissues in ways that are highly coordinated to affect marked changes in nutrient partitioning among these tis-

TABLE 3. *Biological effects of somatotropin in farm animals during growth and lactation*

Tissue	Physiological Process Affected
Skeletal muscle (growth)	↑ Protein accretion
	↑ Protein synthesis
	↑ Amino acid and glucose uptake
	↑ Partial efficiency of amino acid utilization
Bone (growth)	↑ Mineral accretion paralleling tissue growth
Mammary tissue (lactation)	↑ 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	↓ Glucose uptake and glucose oxidation
	↓ Lipid synthesis if in positive energy balance
	↑ Basal lipolysis if in negative energy balance
	↓ Insulin stimulation of glucose metabolism and lipid synthesis
	↑ Catecholamine-stimulated lipolysis
	↑ Ability of insulin to inhibit lipolysis
	↓ GLUT4 translocation
	↓ Transcription of fatty acid synthase gene
	↓ Adipocyte hypertrophy
	↑ IGF-I mRNA abundance
Liver	↑ Glucose output
	↓ Ability of insulin to inhibit gluconeogenesis
Intestine	↑ Absorption of calcium and phosphorus required for milk (lactation) or bone (growth)
	↑ Ability of 1,25-vitamin D_3 to stimulate calcium binding protein
	↑ Calcium binding protein
Systemic effects	↑ Circulating IGF-I and IGFBP-3
	↓ Circulating IGFBP-2
	↓ Amino acid oxidation and blood urea nitrogen
	↓ Glucose clearance
	↓ Glucose oxidation
	↓ Response to insulin tolerance test
	↑ NEFA oxidation if in negative energy balance
	↑ Cardiac output consistent with increases in milk output (lactation)
	↑ Enhanced immune response

↑, Increase; ↓, decrease; IGF-I, insulin-like growth factor I; IGFBP, insulin-like growth factor binding protein; NEFA, nonesterified fatty acids. [Adapted from References 15, 19, 62, 65, 68, 146.]

sues. The biological effects of somatotropin can be broadly classified as either somatogenic or metabolic. The somatogenic effects are those in which ST stimulates cell proliferation. These effects are mediated by IGF-I (155). Many of the metabolic effects are a direct action of ST that involve a variety of tissues and the metabolism of all nutrient classes: carbohydrate, lipid, protein, and minerals (see Table 3). These coordinated changes in tissue metabolism alter nutrient partitioning and thus play a key role in increasing growth performance or milk yield.

The principal effect of ST is on partitioning of absorbed nutrients. In lactating cows or growing cattle treated with bST, digestibilities of dry matter, carbon, nitrogen, and energy are not altered (15, 26, 37, 61). The energy expenditure for maintenance or the partial efficiency of milk synthesis is not altered in dairy cows treated with bST (108, 170). Likewise, studies with growing pigs and cattle have shown that the energetic efficiency of specific processes is not altered. However, maintenance costs at a given body weight are increased by pST administration in pigs that is consistent with the fact that pST-treated animals have a greater proportion of lean tissue (27, 32, 176, 177).

The remainder of this review discusses the mechanisms by which ST exerts its biological effects. The objective is to provide an overview of the mechanisms; many previous reviews have addressed more specific aspects of ST action in domestic animals (19, 62, 65, 137).

A. Effects on Lipogenesis and Lipolysis

Somatotropin has dramatic effects on adipose tissue and lipid metabolism (Table 3). Both lipogenesis and lipolysis are altered by ST treatment, with effects on lipid synthesis being of major importance if animals are in positive energy balance, whereas effects on lipolysis predominate when animals are at an energy balance near zero or negative. In addition, the effects of ST on lipid metabolism are chronic rather than acute. An acute insulin-like effect of ST has been reported in laboratory animal studies with adipose tissue from ST-deficient animals or animal treated with ST antiserum (77, 82, 157, 161). However, this is an experimental paradigm that requires a complete absence of ST as a prerequisite (58). Acute lipolytic effects of ST were also reported in earlier studies (47, 81, 83). Such effects are never observed in domestic animals using more highly purified preparations of ST (19, 26, 68, 99). Rather, ST effects are chronic and predominately involve alterations in the ability of acute homeostatic signals to alter rates of lipogenesis and lipolysis. Furthermore, these effects appear to be a direct action of ST on adipose tissue, because essentially all effects that occur with in vivo ST treatment can be mimicked when adipose tissue explants are cultured chronically with ST (19, 68).

Effects of ST on lipid synthesis are of special importance in growing animals because they generally have substantial rates of fat deposition, especially during the phase of the growth curve that precedes market weight (68). For example, in growing pigs between ~50 and 100 kg body weight (market weight), there is a precipitous increase in lipid accretion rate (Fig. 4; Ref. 70). During this period, ~120–350 g/day of lipid is synthesized and deposited daily in adipose tissue (66–68). Because pigs typically consume diets that are quite low in fat (~9% of calories vs. ~34% of calories for human diets), the majority (~80%) of lipid in the body is derived from de novo fatty acid synthesis (141), and adipose tissue is the major site of conversion of excess energy to fatty acids in both pigs and cattle (12, 141). The extent of this is illustrated by isotope kinetic studies that have shown that >40% of whole body glucose turnover is being used by adipose tissue for de novo lipogenesis in 80-kg pigs (57).

One mechanism by which somatotropin alters nutrient partitioning is to modulate tissue responsiveness to insulin. Somatotropin treatment reduces whole body glucose response when insulin tolerance tests are conducted (56, 84, 158). This effect of ST is frequently referred to as insulin resistance, but this is somewhat misleading since the effect is clearly tissue specific and relates to only

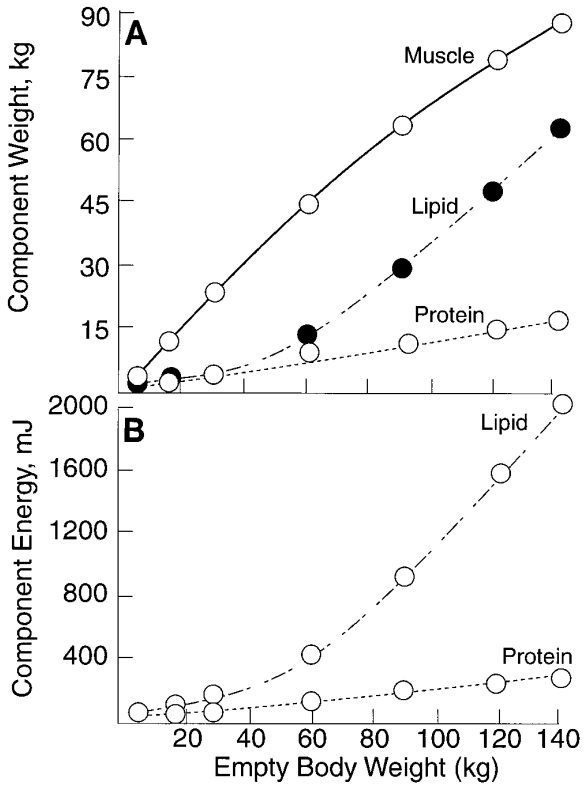

FIG. 4. Changes in protein and lipid accretion that occur during growth of pigs. [Adapted from Shields et al. (160).]

certain insulin-responsive processes. Kinetic studies have demonstrated that the alteration in glucose response to insulin is almost exclusively related to effects on lipogenesis in adipose tissue (57). In contrast, ST treatment does not reduce the ability of insulin to inhibit lipolysis in adipose tissue (56, 158), stimulate rates of protein synthesis in adipose tissue (174), or stimulate glucose uptake and protein synthesis in muscle (56, 186). This exquisite orchestration of glucose partitioning by ST reduces glucose use for fat deposition in adipose tissue, thereby allowing sufficient glucose to support the increase in muscle protein synthesis in growing animals or the increase in milk synthesis in lactating animals.

Somatotropin administration dramatically reduces fatty acid synthesis in adipose tissue as illustrated by results from both in vitro (178–180) and in vivo kinetic studies (57). In growing pigs, rates of de novo synthesis can be decreased by >90%, whereas effects on rates of lipolysis are minimal. The reduced ability of insulin to stimulate lipogenesis in adipose tissue involves a change in the sensitivity (increased ED_{50}) with no change in the maximum response (Fig. 5; Refs. 68, 69). This leads to a marked decrease in insulin-regulated events such as glucose transport, lipogenic enzyme activities, expression of lipogenic enzyme genes, and lipid synthesis (see Refs. 51, 90, 115, 121, 125, 133, 174, 179).

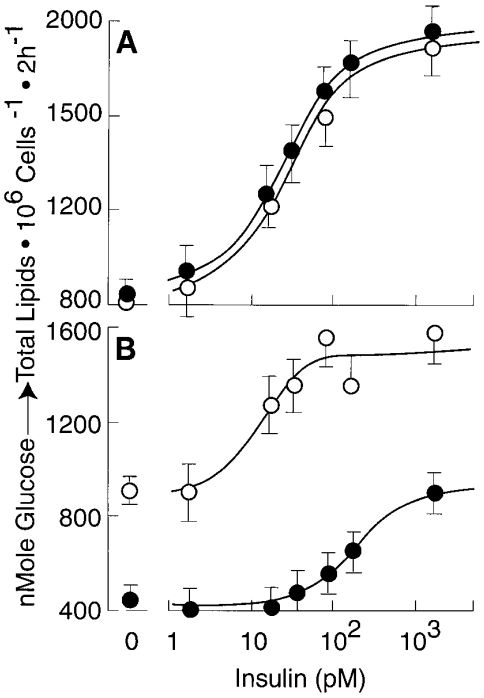

FIG. 5. Dose-response curves for insulin-stimulated lipogenesis in adipose tissue explants from pigs treated daily with vehicle (*A*) or pST (70 μg/kg body wt; *B*) for 0 (○) or 7 days (●). [Adapted from Walton and Etherton (178).]

Recent evidence suggests that there may be appreciable specificity in the ST signal pathway(s) that mediate the anti-insulin-like effects on glucose utilization. This point is illustrated by the observation that the effects of pST on GLUT4 gene expression are different than observed for expression of the fatty acid synthase (FAS) gene in pig adipose tissue (51). Specifically, the effects of pST to reduce FAS gene expression are of much greater magnitude than observed for expression of the GLUT4 gene. There is other evidence that corroborates this observation. Porcine ST selectively affects the activity of certain lipogenic enzymes more than others (90, 125). For example, pST markedly reduces FAS and acetyl-CoA carboxylase enzyme activities in adipose tissue; however, the reduction in activity of enzymes in the pentose cycle is considerably less (see Table 4). Further evidence to support the idea that pST exerts differential effects is based on metabolic studies that have been recently conducted (51). These data revealed that the antagonistic effect of pST on insulin action is more potent when glucose transport is maximized (5 mM glucose) than when glucose concentration limits glucose entry into the cell (i.e., at 1 mM glucose). This suggests that the effects of pST on lipogenesis are manifested predominantly subsequent to glucose transport. This does not mean that pST does not decrease glucose transport, since pST clearly reduces glucose uptake in pig adipocytes (125). However, it appears that the effects of pST on glucose transport are secondary to changes in glucose utilization that occur at key metabolic regulatory points subsequent to transport.

The decrease in insulin sensitivity caused by pST in pig adipose tissue is not associated with any change in insulin receptor number or tyrosine kinase activity of the insulin receptor (125). This is consistent with the fact that some effects of insulin in the adipocyte are not diminished by ST treatment (e.g., insulin inhibition of lipolysis). Little is known, however, about the postreceptor events that mediate the effects of pST on the insulin signal pathway(s) to antagonize the stimulatory effect of insulin on expression of lipogenic enzyme genes. Because of this, studies have been undertaken to use the FAS gene as a model to study how ST reduces insulin signaling. This gene is useful to study, since changes in enzyme activity are the result of changes in enzyme protein mass that reflect changes in FAS mRNA abundance (reviewed in Ref. 94). In addition, changes in enzyme activity (reflecting changes in gene transcription) are quite sensitive to alterations in insulin status (94). Because FAS is under exquisite insulin regulation, it is amenable to investigate whether ST affects insulin signaling to the gene. On the basis of the evidence presented previously, it is not surprising that treatment of growing pigs with pST dramatically decreases FAS mRNA levels and FAS enzyme activity in adipose tissue (51, 90, 125) (see Table 4). Recently, we have found both in rat

TABLE 4. *Effect of pST on various lipogenic enzyme activities in pig adipose tissue*

Study	Control	pST
Magri et al. (125)		
Fatty acid synthase	4.9	<0.1
Glucose-6-phosphate dehydrogenase	157	80
6-Phosphogluconate dehyrdrogenase	117	105
Malic enzyme	173	66
Harris et al. (90)		
Acetyl-CoA carboxylase	8.5	1.8
Fatty acid synthase	27	9
Glucose-6-phosphate dehydrogenase	142	67
6-Phosphogluconate dehyrdrogenase	160	84
Malic enzyme	303	184
Liu et al. (121)		
Acetyl-CoA carboxylase	2.0	0.9

Data presented are expressed in different units depending on the study. Reader should look at original papers for further details.

liver and cultured 3T3-F442A adipocytes that ST reduces FAS mRNA abundance as the result of a decrease in gene transcription (52, 187), indicating that the reduction in FAS mRNA in pig adipocytes also is due to a decrease in transcription. We are unaware of studies, however, that have addressed this question in porcine or bovine adipocytes. In large part, this reflects the difficulties of isolating nuclei from these adipocytes to conduct the run-on transcription analyses and that to date no studies have been reported in which these cells have been transfected with a chimeric gene containing the FAS promoter linked to a reporter gene. Nonetheless, it seems reasonable to speculate that FAS transcription in pig adipocytes may respond to ST in a similar manner.

A fundamentally important question that needs to be answered is, How does ST interfere with insulin signaling? With the use of FAS as a model enzyme gene and with the presumption that this is applicable to the other key insulin-regulated lipogenic enzyme gene, acetyl-CoA carboxylase, the following hypotheses emerge: *1*) the reduction in FAS gene transcription is the result of ST interfering with insulin signaling at some point between the insulin receptor and the gene; *2*) there is a ST response element in the FAS gene promoter that acts as a negative control element to repress insulin-regulated transcription and interacts with key transcription factors that are ST regulated (in this case there is a ST signal pathway to the gene); or *3*) both of these regulatory scenarios occur. At this juncture, it is not possible to clarify which of these alternatives account for the suppressive effects of ST on insulin stimulation of lipogenesis. Recently, Argetsinger et al. (5) reported that ST stimulates tyrosyl phosphorylation of insulin receptor substrate (IRS)-1, which is a key molecule in insulin signal transduction pathways (136). Some have interpreted these findings to suggest that ST signaling involves IRS-1; however, it is difficult to reconcile how tyrosyl phosphorylation of IRS-1 by ST can attenuate insulin signaling when many of the insulin signaling events seem to be associated with insulin receptor-dependent tyrosyl phosphorylation of IRS-1 and subsequent IRS-1 (and IRS-2)-dependent transmission of insulin signaling to downstream components of the insulin signal transduction pathways (136). It is interesting to note, however, that another member of the cytokine family (of which ST is a member), tumor necrosis factor-α (TNF-α), has been shown to induce insulin resistance in obesity (95, 105). The particularly intriguing aspect of these results is that TNF-α induces serine phosphorylation of IRS-1 that seems to interfere with insulin-induced tyrosine phosphorylation of IRS-1 and, hence, attenuate insulin receptor signaling (105). Whether ST mimics the effects of TNF-α remains to be determined.

Somatotropin affects lipolysis indirectly through alterations in adipose tissue response to acute homeostatic signals that regulate lipolysis. This allows for greater mobilization of reserves in ST-treated animals when energy is in short supply (Table 3). This is especially important during ST treatment of lactating cows, because animals are generally near zero energy balance when bST treatment is initiated, and voluntary intake does not match the enhanced milk energy output during the initial phase of the treatment (18, 170). However, ST effects on lipid mobilization are also observed in growing animals when energy intake is restricted (59, 123, 148). Isotope kinetic studies have demonstrated that the extent of the increase in fatty acid mobilization with ST treatment is highly correlated with net energy balance and circulating concentrations of nonesterified fatty acids (NEFA) (18, 59). Elevated circulating NEFA concentrations are occasionally observed when ST-treated animals are in positive energy balance. In this case, the elevated NEFA concentrations relate to the enhanced lipolytic response to homeostatic signals in ST-treated animals and represent a transitory increase relating to the mild stress associated with blood sampling (25).

The regulation of lipolysis involves cAMP and a signal transduction system that includes stimulatory G proteins (G_s) and inhibitory G proteins (G_i). Catecholamines affect lipolysis through the G_s system, and ST treatment dramatically increases the lipolytic response to catecholamines in lactating cows (126, 158) and growing cattle and pigs (25, 140, 148). This is most evident by the increase in circulating NEFA when a catecholamine challenge is administered, and the enhanced response involves an increase in the maximum response (R_{max}) to catecholamines with no change in the sensitivity (Fig. 6). A similar change in the dose-response curve occurs in humans receiving ST treatment (20). This change in the response to catecholamines is evident within 15 h after the initiation of ST treatment (100) and is observed regardless of whether animals are in a positive or negative net energy balance.

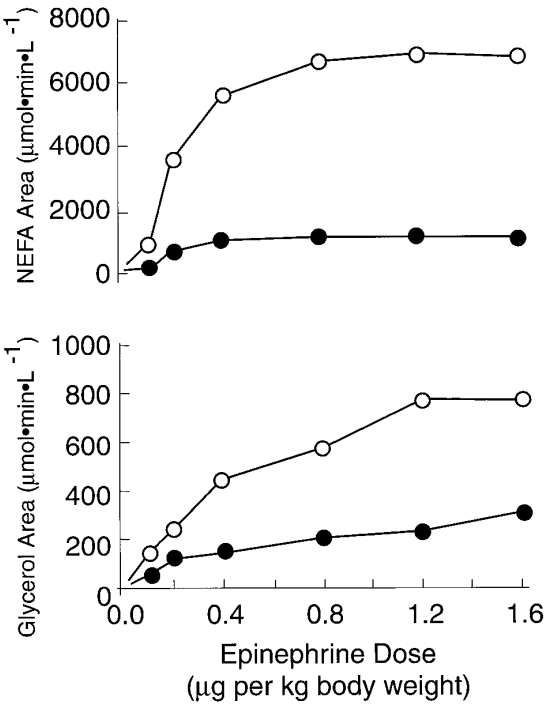

FIG. 6. Response of plasma nonesterified fatty acid (NEFA) and glycerol concentrations to varying doses of epinephrine during bST (○) or excipient (●) treatment periods. Epinephrine challenges were administered intravenously twice each day (1000 and 1400 h) on *days 6–11* of bST treatment (total 12-day treatment period). Response was determined over 20 min postinfusion. [Adapted from Sechen et al. (158).]

Initial studies to examine the mechanism made the surprising observation that the chronic treatment with ST in vivo had no effect on the response of subcutaneous adipose tissue to catecholamines in vitro. Although differences between adipose tissue depots represented a possible partial explanation (175), it became clear that the basis for this paradox lay elsewhere. Somatotropin treatment, in vivo or in vitro, resulted in only modest changes in β- and α_2-adrenergic receptor numbers (53, 54, 97, 181). Furthermore, examination of the G_s proteins and other downstream components of the lipolytic signal transduction cascade demonstrated no differences in adipose tissue from bST-treated and control animals (54, 97). These results raised the possibility that the major mechanism by which ST altered lipolysis might involve the antilipolytic system of adipocytes. Adenosine was a likely candidate because it is an autocrine/paracrine factor that exerts an acute antilipolytic effect via the G_i system. Indeed, chronic treatment with ST decreases the antilipolytic effects of adenosine in adipose tissue (53, 54, 96, 115).

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. 7; Refs. 96, 115). However, the mechanism did not involve a change in binding affinity or adenosine receptor number (54, 97, 181). Studies with adipose tissue from lactating cows and growing sheep also demonstrated that ST treatment did not alter the abundance of the α-, β-, or γ-subunits or the heterotrimeric G_i proteins that bind to the adenosine receptors (54, 96). However, the functionality of the G_i proteins, as assessed by their ability to be ADP-ribosylated by pertussis toxin, was significantly reduced with ST treatment (96). Chronic exposure to ST also prevented the inhibitory effect of low concentrations of guanosine 5′-($\beta\gamma$-imido)triphosphate, suggesting that the ability of the α-subunit of G_i to interact with adenylyl cyclase was impaired (173). Prostaglandins are additional local controls with the E series known to be antilipolytic via the G_i system in rats and humans. Just as with adenosine, ST treatment causes a decreased antilipolytic response to PGE and also decreased PGE_2 production in studies involving microdialysis of subcutaneous adipose tissue of sheep (54). Overall, results demonstrate that a major mechanism by which ST alters lipolysis centers on the G inhibitory system of adipose tissue. Thus 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.

B. Effects on Carbohydrate Metabolism

Somatotropin has numerous tissue effects related to carbohydrate metabolism (see Table 3). This is of particular importance in the dairy cow in which glucose originates almost exclusively from gluconeogenesis and typically 60–80% of the glucose turnover is used for milk synthesis. Treatment of cows with bST increases the rate of glucose irreversible loss and reduces whole body glucose oxidation (18). These adaptations in glucose produc-

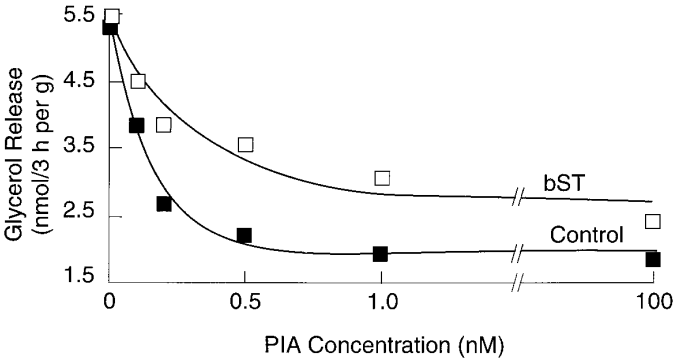

FIG. 7. Inhibition of isoproterenol-stimulated lipolysis by the adenosine analog phenylisopropyladenosine (PIA). Cows received daily injections (40 mg) of bST (□) or excipient (■) for two 8-day periods. Adipose tissue was biopsied on *day 8*, and tissue explants were incubated for 3 h in presence of 10^{-5} M isoproterenol. [Adapted from Lanna et al. (115).]

tion and oxidation in bST-treated cows are quantitatively equal to the extra glucose required for the increased milk synthesis (18). Hepatic rates of gluconeogenesis are increased with ST treatment of dairy cows as demonstrated by in vivo (42) and in vitro studies (109, 149) (Table 3). Mechanisms include a decreased ability of insulin to inhibit gluconeogenesis (42) (Table 3). Thus the reduction in hepatic response to insulin in bST-treated cows allows the liver to sustain an increased rate of gluconeogenesis that is critical to support the increase in the synthesis of milk components. In contrast, ST treatment had no effect on liver glycogen concentration in lactating cattle in positive energy balance (149), although ST treatment did induce a small decrease in cows in negative energy balance (109). Liver glycogen reserves are too limited to sustain increased glucose output by the liver in lactating cows.

In growing pigs treated with pST, glucose utilization by adipose tissue is markedly reduced as discussed earlier, but use by nonadipose tissues is unaffected (57). If treated pigs are in a postabsorptive state, there is an increase in hepatic output of glucose (84). As with lactating cows, the ability of insulin to decrease gluconeogenesis is attenuated in growing pigs and cattle receiving ST treatment (56, 84).

C. Effects on Protein Metabolism

Considerably less is known about the effects of ST on protein metabolism of domestic animals than for either lipid or carbohydrate metabolism. It is clear that ST treatment increases muscle protein accretion in growing animals and milk protein synthesis in lactating cows (Table 3). However, the precise mechanisms are not clear, and the extent to which the effects of ST on protein metabolism are direct or mediated by IGF-I remains unclear. There is some information that suggests IGF-I may mediate the effects of pST on protein accretion (Fig. 2). These results indicate that there is a reasonably good relationship between the changes in circulating IGF-I level and protein accretion rate in pST-treated pigs fed diets varying in dietary protein (Fig. 2). It must be emphasized, however, that these results are associative data and do not provide any insight as to whether the effects of ST on protein accretion are mediated totally or in part by IGF-I.

The enhanced growth rate with ST treatment of ruminants and pigs is due to a more efficient use of absorbed amino acids that is accompanied by a reduction in circulating urea nitrogen concentrations and in urinary nitrogen loss. The increase in protein accretion is largely the result of increased protein synthesis, whereas protein degradation remains unaltered (24, 59, 60, 80, 147, 159). However, some have suggested rates of degradation are decreased (168), and this difference may relate to the methods used to assess degradation.

Somatotropin treatment of growing domestic animals results in a dramatic improvement in the efficiency of amino acid utilization for protein accretion (27, 31). This is frequently referred to as the biological efficiency or partial efficiency of amino acid use. An increase in partial efficiency of amino acid utilization of 25–50% has been reported for pST treatment of pigs (27, 33, 35, 112, 139) and bST treatment of growing cattle (98) and lambs (21, 124). Thus ST both increases the maximal capacity for protein accretion and increases the partial efficiency by which amino acids are used for protein deposition.

Consistent with the improved efficiency of amino acid use, a decrease in blood concentrations of urea nitrogen is consistently observed, demonstrating that whole body oxidation of amino acids is reduced with ST treatment. This has been directly demonstrated in isotope kinetic studies with heifers and steers (59, 60) and from nitrogen balance studies with pigs and ruminants (137). Especially impressive is that the reduced oxidation of amino acids occurs even when protein and amino acid intake are inadequate to meet requirements. Although cellular aspects have not been elaborated, a decrease in hepatic capacity for amino acid catabolism has been observed in bST-treated rats (23).

The effects of ST on muscle histochemistry and morphology have been well characterized (143, 144, 156, 163, 167, 184). Most studies have observed that ST treatment enhances hypertrophy of skeletal muscle fibers without changing muscle fiber number. In response to pST, nuclei proliferation is increased to the same extent as muscle fiber hypertrophy. This event is important because postnatal accretion of DNA is a key factor in regulating muscle growth (3). This increase occurs because of proliferation of satellite cells that reside between the sarcolemma and basement membrane of myofibers. These cells have the ability to fuse with the myofiber and thereby contribute their nucleus to the cell. Thus, during postnatal muscle growth, the increase in muscle DNA is coordinated with the increase in muscle protein. In addition to the effects of ST on protein metabolism, changes also occur in the rate of satellite cell proliferation. Although little information is known for domestic animals, it is clear that satellite cell proliferation is critically regulated by IGF-I. There is considerable information about the effects of IGF-I in laboratory animals and cell culture, and the effects of ST and IGF-I on myogenesis are discussed in depth by Florini et al. (74).

D. Effects on Mammary Gland Metabolism

Treatment with bST causes a dramatic increase in the uptake and utilization of nutrients for the synthesis of milk

(Table 3). However, it has proven to be difficult to document specific mechanisms. At the cellular level, the magnitude of the biochemical changes would likely be small, and mammary epithelial cells, which are actively secreting milk components, are difficult to maintain in vitro because of their high rates of metabolic activity. Nevertheless, the pattern of response to exogenous bST and the change in the shape of the lactation curve (Fig. 3) indicate that bST effects involve both an increase in the rates of milk component synthesis per cell and an improved maintenance of secretory cells. Baldwin and Knapp (8) demonstrated that bST-treated cows had increased protein synthetic capacity as indicated by an increased RNA per gland. Furthermore, Knight et al. (110) observed that the decline in mammary cell numbers that normally occurs during lactation was prevented in goats that received ST for 22 wk.

Several studies have measured the effect of in vivo ST treatment on the activity of key mammary enzymes associated with milk synthesis. Anticipated differences are difficult to detect because methods require using a tissue biopsy, and the mammary glands of ruminants are rather heterogeneous in tissue and cell types. However, studies with cows and goats have reported trends or significant increases in several key enzymes such as acetyl-CoA carboxylase, acetyl-CoA synthetase, and FAS (8, 110, 111, 138). More clear-cut evidence demonstrating the effects of ST on the activity and mRNA level of mammary enzymes comes from studies of rats (10, 11).

Maintaining higher rates of milk synthesis requires a greater nutrient support. Some have suggested that the increase in mammary rates of milk synthesis was merely the consequence of ST effects on nonmammary tissues that allowed for a greater supply of nutrients to the mammary gland (102, 107, 132). However, it is clear that simply increasing nutrient availability by itself does not mimic the effect of bST on lactational performance (30, 146); rather, bST is a homeorhetic control that results in a coordinated series of changes involving both nutrient supply and mammary utilization (Table 3). This coordination includes a diversion of cardiac output and an increase in blood flow to the mammary gland that parallels the magnitude of the milk response to exogenous bST (48, 76).

The mechanism by which ST affects mammary gland function is still uncertain but appears to be indirect, involving the IGF system. As with nonlactating animals, the administration of exogenous bST increases circulating concentrations of IGF-I and IGF binding protein (IGFBP)-3 and decreases circulating IGFBP-2. Furthermore, the magnitude of changes in circulating IGF-I and the IGFBP closely parallels the biological events and the magnitude of the milk responses that occur with bST treatment of dairy cows (see reviews in Refs. 19, 29, 130, 131). In studies with transgenic mice, IGF-I appeared to prevent mammary gland involution after lactation (87). In addition, both IGF-I and des(1–3)-IGF-I stimulate IGFBP production in bovine mammary epithelial cells (128).

There are abundant type I and type II IGF receptors in bovine mammary tissue, and IGF-I addition to bovine cell culture systems increases casein synthesis (30, 43, 49, 86). In contrast, attempts to detect ST receptors in bovine mammary tissue have been unsuccessful (2, 78, 106), and only a very low level of expression of ST receptor mRNA can be detected (79, 88). Close arterial infusion of the mammary gland with bST had no effect on milk yield (127), whereas close arterial infusion of IGF-I or IGF-II stimulates milk yield (150, 152, 154). A role for IGF-I is also consistent with observations that IGF-I dramatically increases blood flow to the mammary gland (150, 153), and this effect appears to be mediated by local production of nitric oxide (114, 151). The lactational response to close arterial infusion with IGFs is arguably the strongest evidence that this is the mechanism for the bST effects on the mammary gland. Nevertheless, lactational responses to close arterial infusion of the 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, the IGFBPs, and their proteases remain to be delineated.

V. SUMMARY

Somatotropin treatment of domestic animals markedly enhances the efficiency of nutrient use and performance. Effects are on postabsorptive use of nutrients and involve an orchestration of many physiological processes in different tissues and organs to enable more nutrients to be used for lean tissue accretion (during growth) or milk synthesis (during lactation). The mechanism by which ST causes these coordinated effects involves tissue-specific changes in key metabolic pathways as well as alterations in tissue response to homeostatic signals. In many cases, the cellular sites of the alterations in metabolic pathways and signal transduction have been identified, and it is clear that the biological effects of ST are dependent on multiple changes. However, the molecular bases of the intracellular ST signal transduction pathways that alter other signaling pathways that are responsible for the homeostatic responses and the mechanisms that account for the tissue-specific effects are obscure. Nevertheless, it is clear than the overall effects of ST are to both enhance the ability of muscle (growth) or mammary tissue (lactation) to utilize nutrients while simultaneously coordinating other physiological processes and tissues (such as adipose tissue), in a manner that supports this enhanced performance. Although we have learned much about the biology of ST in domestic animals during the

past decade, many key questions remain to be resolved. It is likely that as we advance our understanding of ST's mechanism of action we will be able to develop ways to further potentiate the stimulatory effects of ST or identify alternative strategies that increase not only growth performance and milk yield but, more importantly, the efficiency of production.

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