Paradox of BST: Why Cows Don't Burnout

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INTRODUCTION

The improvement of productive efficiency and economic return is an important goal in dairy farming. Because the provision of feed constitutes a major component of farm expenditure, efficiency is often defined as the relationship between output of saleable milk per unit of feed input. In this context, we define productive or biological efficiency as the yield of milk and milk components in ratio to the nutritional cost of maintenance and lactation.

Biological efficiency of a dairy cow increases as milk production increases (3). Maintenance requirements for dietary energy and protein are a substantial proportion of total requirements, but they are constant regardless of the level of milk production. Therefore, the cow producing more milk has to increase intake to support this extra milk, but she also has a higher biological efficiency because a larger proportion of total nutrient intake is used to make milk. This is frequently referred to as a dilution of maintenance and the relationship to level of milk yield is shown in Figure 1. The cow that averages 50 lbs milk/day uses approximately 18% of dietary protein and 38% of dietary net energy to maintain herself whereas these are reduced to 12% and 29% in a cow which averages 75 lbs milk/day.

Somatotropin (ST) is but one of a long line of technologies which improve biological efficiency. Genetic selection, treatment of illness and development of herd health programs,

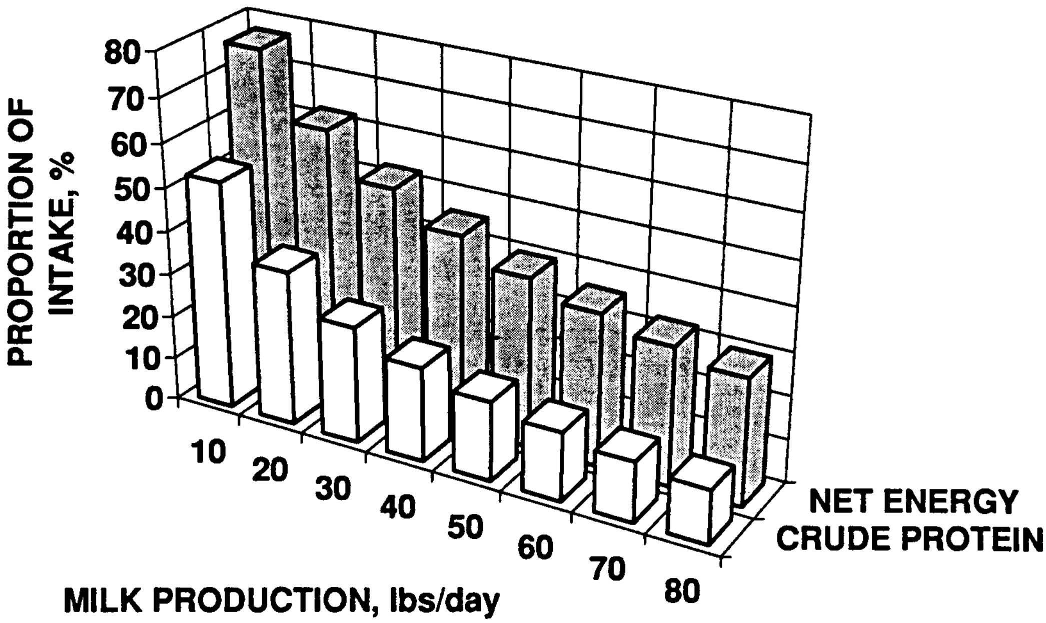

Figure 1. Relationship between level of milk yield and the proportion of nutrients used for maintenance

improvement of milking systems and milking management practices, diet analyses and feeding an adequate balance and amount of nutrients are but a few examples. Because these technologies reduce the resource input and waste output per unit of milk, they are important in terms of profitability, sustainability, competitiveness and environmental impact. With each advance in technology some have claimed that cows would be stressed and burnout; these claims have also been made for somatotropin. Stress and burnout cause cows to produce less milk and have a lower biological efficiency, the exact opposite of what is observed with bST treatment. There are approximately 2000 studies on bST published in the scientific literature and results have been remarkably consistent. Investigations have encompassed the range of management and environmental conditions which characterize world-wide dairy production.

PRODUCTION RESPONSES

There have been almost one hundred technical reviews that have summarized various aspects of the production responses to bST. Obviously, consideration of all technical aspects is outside the scope of this paper but we would refer readers to recent reviews for information related to animal performance and nutrition (6, 8, 9, 12, 20, 21), bioenergetics and metabolism (2, 5, 7, 16, 25) and animal health and well-being (11, 13, 17, 19, 23, 24, 26). These summaries review the published literature and provide citations to specific studies. Suffice to say that considerations for bST-treated cows are essentially identical to those for untreated cows with similar milk production. Of particular importance is the bioenergetic and nutritional studies showing that milk responses to bST treatment have been observed using diets ranging from pasture only to high energy concentrate based feeds. These investigations also show that nutritional requirements of bST-treated cows are the same as those for untreated cows and are a function of the animal's maintenance requirement, body condition and requirements for milk synthesis. Thus, the bioenergetics of bST use represents a clear contrast to the use of thyroprotein; thyroprotein causes stress resulting in an increase in the animals' nutrient requirements for maintenance and milk.

Quality of management will be the major factor affecting the magnitude of milk response to bST (see reviews 1, 3, 12, 13, 20, 21). This concept is qualitatively illustrated in Figure 2. Facets that constitute the quality of the overall management program include the herd health program, milking practices, nutrition program and environmental conditions. Several long-term studies have had management so inadequate that a near zero response was observed with bST supplement. The study by Hoogendoorn et al. (14) serves as an example because the quality of nutritional management varied over the course of the 26-wk treatment period. Cows were fed only pasture, and milk responses to bST were greatest (+18%) in the spring when pasture supply was adequate, declined to zero during the summer drought, but were again significant during the fall when pasture supply was good. *Bovine somatotropin is not magic!* If cows are given an inadequate amount of feed or are fed a diet without adequate nutrient balance, then the magnitude of response to bST will decrease according to the extent of the inadequacy (Figure 2).

There are several apparent paradoxes concerning somatotropin which need to be considered in developing an understanding of the mechanism of action. The first of these is a comparison of circulating bST concentrations under different situations. As illustrated in Table 1, circulating ST is higher in genetically superior cows and cows treated with

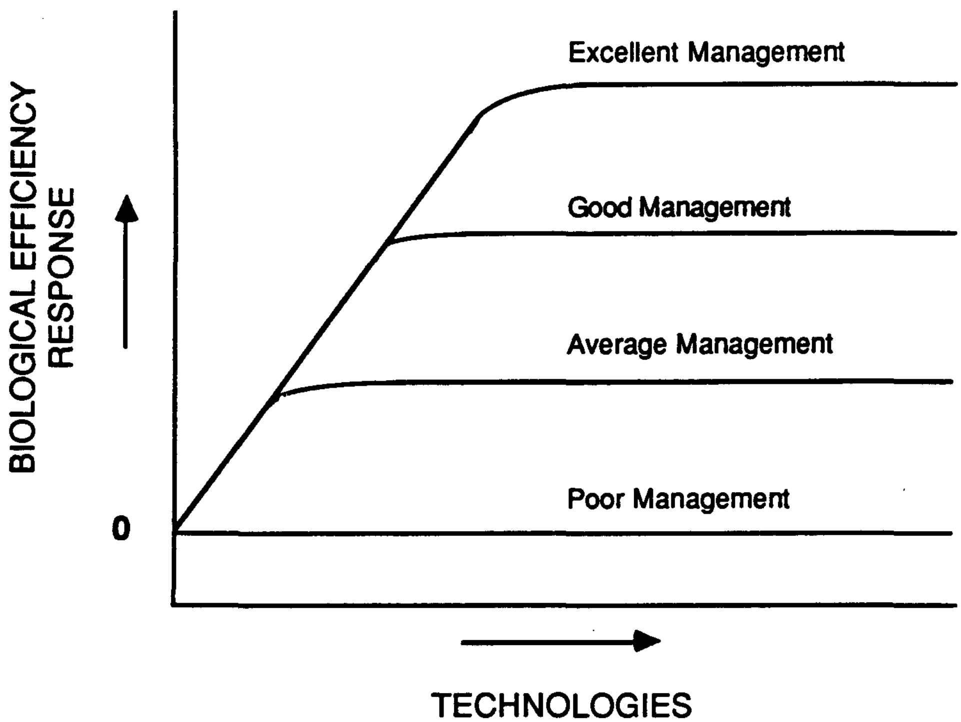

Figure 2. Impact of quality of management on biological efficiency response to bovine somatotropin or other new technologies.

exogenous bST, and this coincides with a high level of milk production. Yet circulating bST is also elevated when an animal is under adverse conditions such as chronic undernutrition or poor management, and in this instance milk yield is low (Table 1). In fact, the easiest way to increase circulating levels of endogenous ST is to starve an animal and that clearly leads to a reduction in milk yield. Thus, the mechanism of ST action must accommodate this paradox and explain how ST can play a key role in regulating metabolism under ideal conditions where an animal is at a high level of performance as well as when the animal is in an adverse environment with a low level of performance.

A second paradox is the fact that response to bST treatment is related to quality of management and in particular to nutritional management as discussed above. This relationship was even apparent in 1937 when Asimov and Krouse conducted their original studies (1). They concluded: *"The practical application of the lactogenic preparations from the anterior pituitary is in general more profitable on a well-run farm than on a farm with a poor food basis or where cattle are kept under unsatisfactory conditions" (1).* Thus, an understanding of the mechanisms of ST action must accommodate the paradox whereby milk response to ST is modulated by quality of management.

A third paradox involves the claim by some that bST treatment would cause catastrophic health effects and burnout. This speculation was based on an erroneous idea of the mechanism of bST and anticipated adverse effects. Metabolic disorders would most likely occur the first few days of bST treatment when milk yield has increased but intake has not. Suffice to say, there is not a single mention of clinical ketosis or milk fever occurring during the first weeks of bST treatment in any of the hundreds of published studies. In fact, studies which have administered bST to cows with inadequate nutrient supply or under poor management conditions have observed no adverse effects, just a negligible milk response (see reviews 1, 2, 3, 12, 13, 20, 21). Furthermore, recent studies have demonstrated that administration of ST to patients suffering from anorexia has beneficial effects (15). Therefore, the mechanism of ST must be consistent with the observations that exogenous ST does not cause burnout or have adverse effects when administered to animals even when they are in an adverse environment and, at least for humans, ST even has beneficial effects when given under conditions of nutritional and/or physiological stress.

Table 1. Paradoxical relationship between circulating somatotropin and milk yield in lactating cows

Physiological Situation	Circulating Somatotropin	Milk Yield
ST-treated	↑	↑
Genetically superior	↑	↑
Inadequate nutrition	↑	↓
Poor management	↑	↓

TABLE 2. Effect of bovine somatotropin on specific tissues and physiological processes in lactating cows.

Tissue	Process affected during first few days and weeks of treatment
Mammary	↑ Synthesis of milk with normal composition
	↑ Uptake of all nutrients used for milk synthesis
	↑ Activity per secretory cell
	↑ Number and/or maintenance of secretory cells
	↑ Blood flow consistent with increase in milk yield
Liver	↑ Basal rates of gluconeogenesis
	↓ Ability of insulin to inhibit gluconeogenesis
	ϕ Glucagon effects on gluconeogenesis and/or glycogenolysis
Adipose	↓ Basal lipogenesis if in positive energy balance
	↑ Basal lipolysis if in negative energy balance
	↓ Ability of insulin to stimulate lipogenesis
	↑ Ability of catecholamines to stimulate lipolysis
Muscle	↓ Uptake of glucose
Pancreas	ϕ Basal or glucose-stimulated secretion of insulin
	ϕ Basal or insulin/glucose-stimulated secretion of glucagon
Kidney	↑ Production of 1,25 vit D_3
Intestine	↑ Absorption of Ca, P and other minerals required for milk
	↑ Ability of 1,25 vit D_3 to stimulate Ca binding protein
	↑ Ca binding protein
Whole body	↓ Oxidation of glucose
	↑ NEFA oxidation if in negative energy balance
	ϕ Energy expenditure for maintenance
	↑ Energy expenditure consistent with increase in milk yield (i.e. heat per unit of milk not changed)
	↑ Cardiac output consistent with increases in milk yield
	↑ Biological efficiency (milk per unit of energy intake)

Adapted from Bauman et al. (5.7). Changes (↑=increased, ↓=decreased, ϕ=no change) which occur in initial period of bovine somatotropin supplement when metabolic adjustments occur to match the increased use of nutrients for milk synthesis. With longer term treatment, voluntary intake increases to match nutrient requirements.

HOMEOSTASIS/HOMEORHESIS

To understand the mechanism of action of somatotropin, a brief review of metabolic regulation is appropriate. Regulation of nutrient partitioning involves two types of controls - homeostasis and homeorhesis (4, 5). Homeostasis involves the operation of multiplex compensatory mechanisms functioning to maintain physiological equilibrium. Cannon originally defined homeostasis as *"the condition of relative uniformity which results from the adjustments of living things to changes in their environment" (4).* Thus, homeostatic controls operate on a minute-by-minute basis so that, despite acute challenges from the external environment, the internal environment remains unchanged. There are many well-established examples of homeostasis. One example for nutrient partitioning deals with the absorptive and postabsorptive periods following the consumption of a meal. In the short-term, homeostatic controls (primarily insulin and glucagon) maintain a relatively constant supply of nutrients to peripheral body tissues by promoting the storage of nutrients following a meal and the mobilization of these nutrients during the postabsorptive period.

The second type of control is called homeorhesis and was defined as the *"orchestrated changes for priorities of a physiological state" (4).* Homeorhetic control involves the coordination of metabolism, resulting in the directed partitioning of nutrients to support requirements specific for each physiological state. We crystallized this concept and related homeorhesis to the regulation of nutrient utilization for the processes of growth, pregnancy and lactation (4, 5). Thus, homeorhetic mechanisms provide chronic regulation, while homeostatic controls operate on an acute minute-by-minute basis to maintain steady state and in life-threatening situations, may even override the long term regulation to preserve vital functions.

We also proposed that mechanisms of the higher-level homeorhetic control involve alterations in response to control functions of homeostasis (4, 5). This allows homeorhetic control to shift nutrient use in support of physiological state, yet accommodate the need for acute homeostatic regulation to preserve steady state. Recent work has shown that this is indeed the mechanism by which nutrient partitioning is shifted under a wide range of physiological situations (5, 7, 25).

MECHANISM OF SOMATOTROPIN ACTION

Somatotropin is a homeorhetic control that shifts the partitioning of nutrients in a lactating cow so that more are used for milk synthesis. This involves coordinating the metabolism of various body organs and tissues and includes the metabolism of all nutrient classes - carbohydrates, lipids, proteins and minerals. Thus, treatment with bST both increases the rate of milk synthesis within the mammary gland and orchestrates other body processes in a manner to provide the necessary nutrients to support this enhanced rate of milk synthesis (see reviews 2, 3, 5, 7, 25). Table 2 summarizes a number of the major coordinated changes which occur with bST treatment of a dairy cow. These adaptations are of critical importance during the initial period of bST treatment when milk yield has increased but intake has not. These adaptations can be broadly divided into two types -

direct effects on some tissues and indirect effects that are thought to be mediated by the insulin-like growth factor (IGF) system.

Direct actions of ST appear to be primarily concerned with the coordination of metabolic processes (see reviews 2, 5, 7, 25). Adipose tissue provides an example to illustrate the mechanisms of action. Adipose tissue has two main functions, lipogenesis and lipolysis. ST treatment has no acute effects on either of these functions, but it does alter lipid metabolism on a chronic basis. Specifically, ST treatment alters adipose tissue response to homeostatic signals affecting lipid synthesis and lipid mobilization. Studies have shown that ST reduces the ability of insulin to stimulate lipid synthesis and enhances the ability of catecholamines to stimulate lipolysis (Table 2). Thus, if the cow is in a positive energy balance when bST treatment is initiated, nutrient use for body fat stores is reduced and these nutrients are redirected in support of the increased milk synthesis. On the other hand, if the cow is near zero energy balance when bST treatment is initiated, then body fat reserves are mobilized to support the nutrient needs for the extra milk synthesis. With prolonged ST treatment, voluntary food intake increases and animals return to a positive energy balance allowing the replenishment of body reserves over the lactation cycle.

The indirect effects of ST appear to be primarily associated with the mammary gland via the actions of the IGF system (see reviews 7, 18). These effects involve an increase in the rate of milk synthesis per cell and an improved maintenance of mammary cells (Table 2). The IGF system is complex involving IGF-I and IGF-II as well as two specific IGF receptor types (10, 18). In addition, the majority of IGFs in physiological fluids are bound to soluble, high affinity binding proteins. There are six specific IGF-binding proteins

(IGFBP) and their postulated roles include serving as circulatory transport vehicles, retarding IGF degradation, facilitating transvascular movement, providing an extravascular pool, and/or modulating directly the actions of IGFs at specific target cells either by enhancing or blocking their activity. Administration of bST to lactating cows causes an increase in circulating concentrations of IGF-I and IGFBP-3 and a decrease in IGFBP-2.

INTEGRATION

Nutritional status plays a key role in the regulation of IGFs and their binding proteins (see reviews 10, 18). We do not fully understand how the IGF system mediates mammary function. However, it is apparent that changes in circulating concentrations of IGF-I and some of the IGFBPs are closely tracking the biological events and the magnitude of milk responses that occur with bST treatment. In the lactating dairy cow, moderate undernutrition has no effect on basal concentrations of circulating IGF-I, but administration of bST results in a less dramatic increase in circulating IGF-I compared to the situation when animals have an adequate nutritional status (Figure 3). When nutritional status is severely compromised by a short term fast, basal concentrations of IGF-I are lower and the ability of bST to increase IGF-I is abolished (Figure 3). A similar impact of nutritional status on the somatotropin/IGF system is observed in growing cattle and other species including humans (7, 10, 18). Although not as extensively investigated, basal and bST-stimulated levels of IGFBP also appear to be modulated by nutritional status.

The relationship between nutritional status and the ST/IGF system also provides a framework to consider variations in milk response to bST and the paradoxes which were

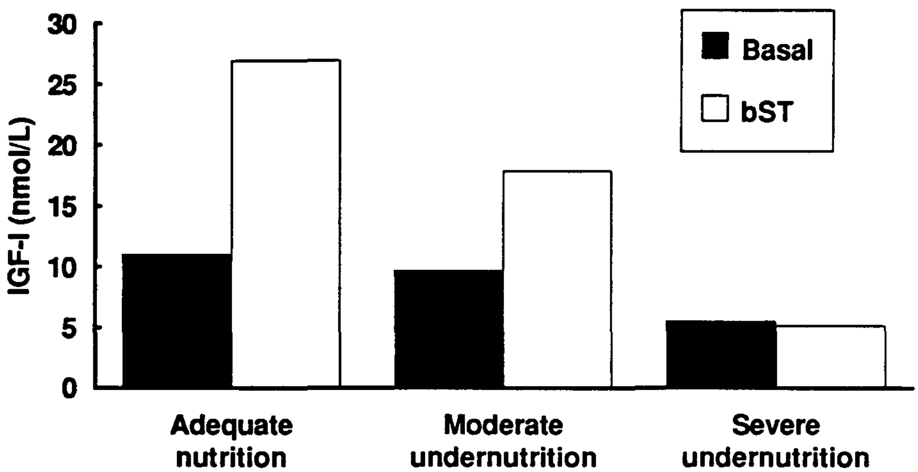

Figure 3. Circulating concentrations of insulin-like growth factor-I (IGF-I) in lactating cows receiving adequate nutrition (120% of requirements), moderate undernutrition (80% of requirements) or severe undernutrition (two days of feed deprivation). Values represent averages obtained during basal conditions and 18 to 24 h after a single subcutaneous injection of bovine somatotropin (bST; 40 mg). The SEM was 1.5 nmol/L.

discussed earlier. A conceptual model of this relationship is presented in Figure 4.

Moderate undernutrition attenuates both the increase in circulating IGF-I and milk yield in response to bST. Cows in early lactation are typically in substantial negative energy balance and have higher circulating concentrations of endogenous ST but lower basal levels of IGF-I; short-term bST treatment results in much lower responses in circulating IGF-I and milk yield than found in cows during later lactation. Thus, the direct actions of ST on tissues such as adipose occur in early lactation to maximize nutrient supply to the mammary gland, but the ST/IGF system is attenuated by nutritional status (Figure 4). Similarly, the magnitude and maintenance of the milk response to long term treatment with bST is related to nutritional status and the quality of management. As mentioned earlier, studies in which bST was administered to cows with inadequate nutrient supply or under poor management conditions have observed no adverse effects, but milk response to bST was negligible. In chronically underfed animals, levels of endogenous ST are high and the direct effects are to partition nutrients away from storage in adipose tissue toward utilization, but effects on the IGF system are uncoupled so that use by the mammary gland is not stimulated (Figure 4). Therefore, these adaptations alter metabolism in a manner which is beneficial for the animal's survival and minimize use of nutrients for milk production during feed inadequacy. Overall, nutritional regulation of the ST/IGF system appears to be a key component signalling the appropriate use of nutrients; without these coordinated responses to nutrient supply, use of nutrients for productive functions could compromise animal well-being and health.

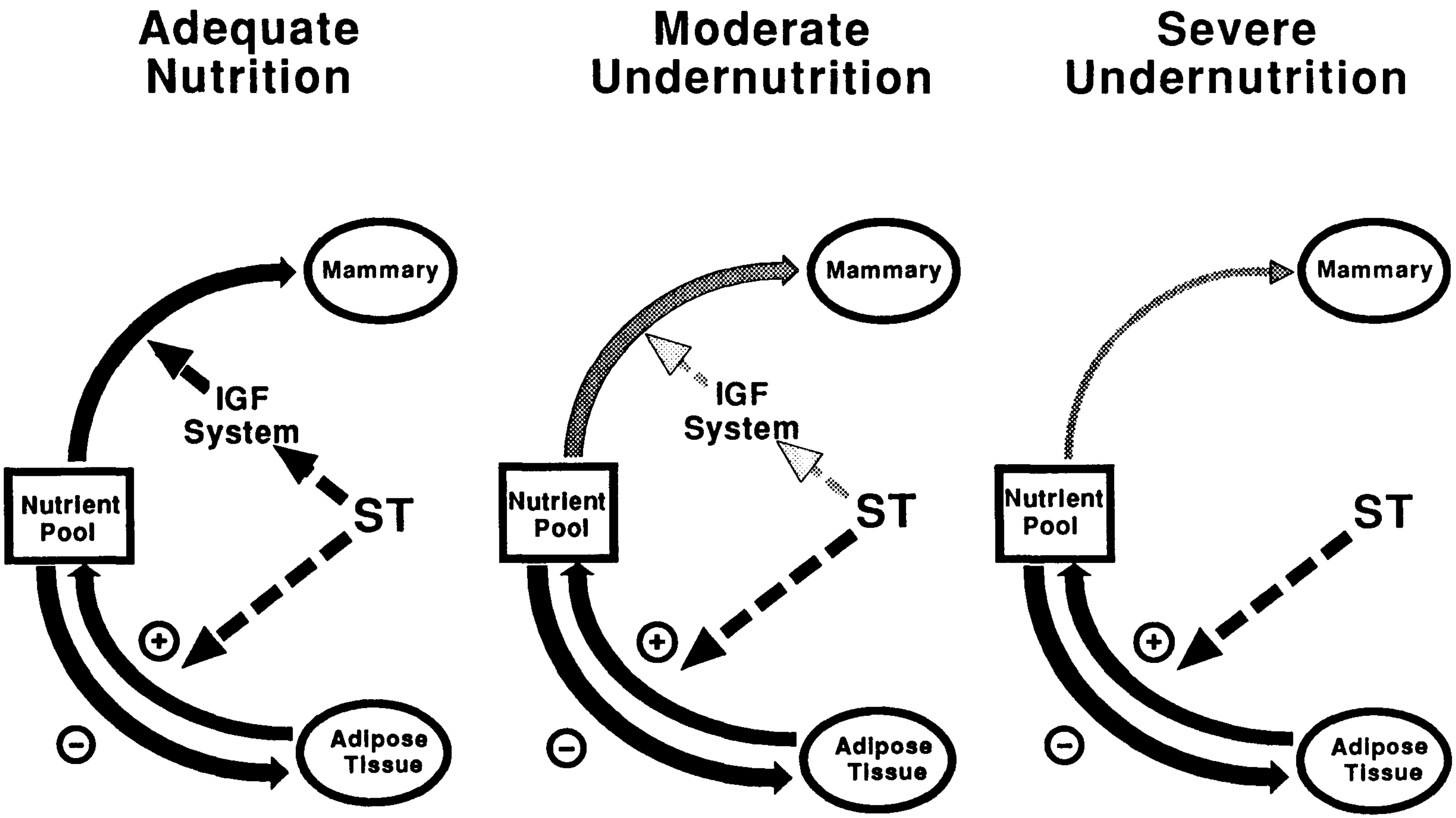

Figure 4. Conceptual model illustrating the effects of somatotropin (ST) and nutritional modulation of the ST/insulin-like growth factor (IGF) system. Direct effects of ST include alterations in activities of key enzymes and tissue response to homeostatic signals as represented by plus and minus symbols on adipose tissue rates of lipolysis and lipogenesis, respectively (Bauman and Vernon, 7). Indirect effects involve the IGFs and their binding proteins, and these are modulated by nutritional status, as indicated (McGuire et al.,18).

CONCLUSIONS

Somatotropin treatment of dairy cows results in a remarkable increase in milk yield and an unprecedented gain in biological efficiency (milk per unit of feed). Aspects of the production responses including effects on nutrition, bioenergetics, metabolism and animal well-being have been extensively examined over a wide range of management and environmental conditions. Quality of management is a major factor affecting the magnitude of milk response to bST. Overall, somatotropin is a homeorhetic control that increases rates of milk synthesis by the mammary gland and coordinates a series of physiological adaptations in a variety of tissues to support nutrient needs for milk synthesis. These tissue adaptations include the activities of key enzymes and alterations in tissue response to homeostatic signals. In addition, nutritional regulation of the ST/IGF system appears to be a key component signalling the appropriate use of nutrients and this plays a key role in animal performance and well-being across a range of physiological situations.

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