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Metabolic Modifiers for Use in Animal Production

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Summary

Metabolic modifiers are a group of compounds that alter the physiology and metabolism of animals in specific ways to improve efficiency of meat and milk production and, in certain instances, to improve yield and composition of animal-derived products. These metabolic modifiers include

- *anabolic*[1] *implants* for finishing beef cattle,
- *beta-adrenergic agonist* (ß-agonist) feed additives for finishing swine and beef cattle, and
- *somatotropin* (ST) growth hormones administered to lactating dairy cattle and swine.

Applications of these metabolic modifiers and related technologies in the United States are approved for a number of species by the U.S. Food and Drug Administration's (FDA) Center for Veterinary Medicine and date back to 1956 for the use of anabolic implants in cattle.

Anabolic implants for beef cattle contain naturally occurring steroid hormones or *synthetic analogues* used as single-compound or combination commercial products. New implant products have been developed during the past four decades, some most recently approved in 2004. More than 90% of beef cattle in the United States receive implants during the growing–finishing phases of production. The continued long-standing use of implants is evidence of their economic value to producers. Adherence to prescribed use poses no negative impact on animal well-being or on the quality and safety of beef and beef products.

The ß-agonist feed additive ractopamine was approved by the FDA in 1999 for use in finishing swine and in 2003 for use in finishing cattle. The commercial products Paylean for swine and Optaflexx for cattle are the only ß-agonists available in the United States. A similar product, Zilmax, is approved for use in Mexico and South Africa. These commercial products enhance carcass lean content and feed efficiency when fed as prescribed during the last 28–42 days (d) before harvest.

Bovine somatotropin (bST) is a naturally occurring protein hormone now produced by recombinant DNA technology. The FDA approved administration of bST to lactating dairy cattle in 1994. Rates of milk synthesis and secretion are increased, resulting in improved marketable milk yield. Feed intake is increased to accommodate the increased nutrient demand, without need for special diets and without negative effects on reproductive performance or lifetime productivity of the cow. Nutrient composition and manufacturing properties of the milk are not

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[1]Italicized terms are defined in the Glossary.

altered. Approximately one-fourth of dairy cows in the United States currently receive bST.

Porcine somatotropin (pST) is similar to bST but differs in amino acid composition, providing specificity of action among species. When pST is administered to growing pigs, coordinated shifts in metabolism occur, resulting in increased muscle and decreased fat accumulation in the carcass. Feed efficiency is improved, in part by decreased feed intake, and nutrient excretion is decreased markedly. Effects are dose-dependent, and although it is not FDA-approved for use in the United States, the commercial product Reporcin is approved for use in Australia and several other countries.

Additional technologies currently are being investigated for efficacy and safety in meat-producing animals but have not been approved by the FDA. These technologies include *immunomodulation*, such as a vaccine (Improvac) that increases growth rate and decreases the boar taint common in pork from pigs raised to market weight as intact males. *Plasmid vector administration* of growth-hormone-releasing hormone in the muscle of animals shows promise as another new technology for achieving effects similar to those observed with ST administration. The ultimate benefit of currently approved metabolic modifiers and successful development efforts under investigation or review is enhanced sustainability and profitability of livestock production. Benefits are shared by producers, processors, and consumers.

This paper describes the classification, characteristics, and effects of metabolic modifiers approved for use in animal production. Topics include *estrogenic* and *androgenic* agents for beef cattle, ß-agonist mechanisms of action and safety of oral administration to meat animals, and the efficacy and safety of somatotropin. The paper also presents the current status of metabolic modifier approval around the world.

Introduction

Sustainability of food-animal production requires maintenance of excellent animal health, minimization of negative impact on the environment, and efficient use of natural resources to minimize costs. Animal welfare and safety of the food produced also must be assured. The cost of feed represents approximately 70% of animal production costs. Therefore, the efficiency with which food-producing animals convert feed to edible product is critically important. Some improvement in feed efficiency is achieved through genetic selection, but this complex trait is influenced by a multitude of genes, precluding to date the use of single- or specific-gene selection strategies. Improved understanding of nutrition and animal metabolism of nutrients has resulted in the development and use of metabolic modifiers for altering composition of gain and for enhancing the efficiency of meat and milk production. Technologies for the synthesis and delivery of metabolic modifiers first were developed more than 50 years (yr) ago, but they still are being investigated actively today.

Metabolic modifiers are compounds that alter the biochemical pathways regulating nutrient use for growth and lactation. Metabolic pathways targeted for intervention include those for protein synthesis and protein *turnover* in skeletal muscle, for lipid synthesis and lipid turnover in *adipose tissue* (fat), and for regulation of milk synthesis and secretion in the mammary gland. Certain metabolic modifiers alter the relative rates of muscle and adipose tissue growth to improve carcass composition when animals are harvested for meat, and others are used only to improve lactation performance. Most metabolic modifiers decrease the proportion of nutrients that are excreted relative to that retained in the body.

Metabolic modifiers include naturally occurring hormones, synthetic steroid hormone analogues, and synthetic phenethanolamine compounds called ß-agonists. Somatotropin is administered to lactating dairy cows to enhance the yield and efficiency of milk production. Two natural steroid hormones, estradiol and testosterone, improve growth rate and efficiency of growth in cattle. The synthetic ß-agonist compounds are administered orally in the feed near the end of the finishing phase of growth to enhance carcass composition and growth performance in pigs and cattle. Beta-agonists do not enhance milk production and are not approved for use in lactating dairy cattle.

Classes and Effects of Metabolic Modifiers

Estrogenic and Androgenic Agents for Beef Cattle

Estrogenic and androgenic growth-promoting agents have been used safely in beef production since first approved in the United States in 1956 by the FDA. Six individual compounds are approved for use either alone or in combination. Doses of individual compounds vary among the several approved combination implants.

Estrogenic products are effective in steers, androgenic products are effective in heifers; combination products also are effective. These products have not been shown to be effective in swine, and none has been approved by the FDA for this species (Hancock, Wagner, and Anderson 1991).

A combination implant containing estradiol benzoate and progesterone (Synovex-S) was approved in 1956 for use in beef cattle, and the combination of estradiol benzoate with testosterone propionate (Synovex-H) was approved in 1958, again for beef cattle. Zeranol, or alpha-zearalanol, the only compound approved for cattle and lambs, was approved in 1969 under the trade name of Ralgro. One orally administered compound, melengestrol acetate, a synthetic progestagen (Pfizer of Kalamazoo, Michigan), was approved in 1977. Six product approvals were granted in the 1980s, including estradiol-17ß alone (Compudose) and trenbolone acetate alone (Finaplix). Commercial product combinations of various amounts of estradiol and trenbolone acetate followed, with the most recent approvals granted in 2003 and 2004.

Detailed descriptions of the chemistry and mechanisms of action of estrogenic and androgenic compounds have been published (Hancock, Wagner, and Anderson 1991; NRC 1994). These anabolic agents increase rates of muscle protein synthesis and deposition and decrease the amount of lipid at a particular live weight (NRC 1994, 2000). Although implants increase feed intake by 5–10%, they decrease the amount of energy required for maintenance, increasing the amount available for growth and thereby improving feed efficiency by 5–15%. Daily gain is improved by up to 25% when aggressive implant strategies are used in cattle fed high-concentrate diets (Bartle et al. 1992; Johnson et al. 1996; Perry, Fox, and Beermann 1991). Comprehensive summaries of the effects of implant strategies using various combinations of commercial products indicate that, up to a point, increasing the anabolic implant dose increases the weight at which animals reach a common body composition or lean-to-fat ratio (Bartle et al. 1992; Guiroy et al. 2002; NRC 1996). Efficiency of use of absorbed nutrients is improved, leading to a lower nutrient mass excreted per unit of live weight gain when implants are used. A review of possible effects of implant strategies on beef quality concluded that measured either objectively or subjectively, current anabolic implants have subtle, if any, effects on tenderness (Nichols et al. 2002). Where differences have been detected, however, there generally have been slight increases in shear force and decreased tenderness.

All aspects of safety (human as well as animal) and verification of efficacy of anabolic metabolic modifiers must be reviewed and approved for use in the United States by the FDA's Center for Veterinary Medicine before they may be used legally. Each commercial product must be administered according to the label, which includes recommended minimal and maximal days to harvest, but no *withdrawal* is required with use of the anabolic implants. The only approved method of implantation is via *subcutaneous* insertion in the middle third of the backside of the ear. The ears are removed during processing and are not used for human consumption.

The European Union (EU) banned importation of U.S. beef from cattle administered "growth promotants" in 1989. The EU action was affirmed and reaffirmed through risk assessment documents released in 1999 and 2002, principally in response to public concern about involuntary hormone exposure. This action was not supported at the time by either the EU's own scientific committee (the Lamming Committee) or the World Health Organization's joint FAO/WHO Expert Committee on Food Additives, and it may be suggested that the original EU ban was a political risk assessment.

Australia, Canada, New Zealand, and the United States, however, allow use of the same natural and synthetic anabolic hormones in beef cattle. The Australian Pesticides and Veterinary Medicines Authority (APVMA 2003) published results from the extensive review of data produced by EU-commissioned studies regarding the safety of anabolic hormone growth promotant use in cattle. The Authority's independent analysis concluded there was not adequate evidence to support the contention that consumption of residues of those compounds posed adverse health risks—including cancer risk—for humans. They concluded further that there was no justification for reconsideration or change of existing use under approved label conditions or practices in Australia.

Beta-agonists

Beta-agonists are naturally occurring and synthetic organic compounds that share a common chemical structure of compounds classified as phenethanolamines. Several ß-agonists are used therapeutically in human and animal medicine for specific effects on smooth muscle, whereas others were investigated originally as possible

antiobesity agents. Studies revealed that several ß-agonists act as metabolic modifiers with distinctive ability to repartition use of consumed nutrients toward increased skeletal muscle growth and decreased adipose tissue accumulation in growing cattle, swine, broilers, and turkeys (Beermann 1993; Moody, Hancock, and Anderson 2002; NRC 1994). Beta-agonists are orally active and efficacious at 5–30 parts per million (ppm) of feed when fed for short periods of time (28–42 d) near the end of the finishing period. The response diminishes with time, so their use requires careful planning to determine the optimal feeding period. Beta-agonists do not enhance lactation, nor are they approved for use in breeding animals (Moody, Hancock, and Anderson 2002).

Currently only two ß-agonist products are approved by the FDA for use in finishing swine and cattle in the United States, and both contain ractopamine hydrochloride, manufactured by Elanco Animal Health, Greenfield, Indiana. Paylean was approved in December 1999 for use in finishing swine and is approved for use in 21 countries. Optaflexx was approved in June 2003 for use in cattle produced for beef. Another ß-agonist, zilpaterol, is manufactured and sold commercially as Zilmax by Hoechest-Roussel Vet, Wiesbaden, Germany. It is approved for use in beef cattle in Mexico and South Africa, and other countries are considering its approval. Labels on commercial products provide specific feeding guidelines for each approved ß-agonist. None of the ß-agonists that act as a metabolic modifier in animal production are approved for use by the EU (Kuiper et al. 1998).

In the United States, finishing pigs are fed Paylean at rates of from 4.5 to 18 grams (g)/ton (5–20 ppm ractopamine hydrochloride, respectively) from 68 to 109 kilograms (kg) live weight with no withdrawal period. The feed must contain 16% protein to assure nutrient requirements are met when Paylean is fed. Enhanced muscle growth depends on adequate availability of essential amino acids to support the stimulation of protein synthesis (Dunshea and Gannon 1995). Feeding Paylean at 18 g/ton for 30 d increases average daily gain by up to 10%, decreases feed intake by 3–5%, increases carcass yield by 1 kg, and increases carcass muscle content from 52% up to 58% (Dunshea and Gannon 1995; Moody, Hancock, and Anderson 2002; NRC 1994). This increase results in 4.3 kg (10–12%) more lean muscle yield per animal. At a constant carcass weight the separable fat in the carcass is decreased from 27% to 23% of carcass weight, or equivalent to 3 kg less fat. These changes improve feed efficiency and increase the value of the pork carcass without adversely affecting eating quality or processing properties of the meat. Choice of dose used will affect the magnitude of the response, and response does vary somewhat among the different genetic strains of pigs raised for pork.

Optaflexx can be fed to finishing beef cattle at dietary levels of 10–30 ppm for the final 28–42 d of feeding, but the recommended level is 200 milligrams (mg) per head per d for steers (Elanco 2003). This dosage is equivalent to approximately 20 ppm at normal amounts of feed intake observed near the end of the finishing. Results from studies involving more than 4,000 cattle fed Optaflexx demonstrated that average daily gain was improved 15–25% with no change in feed intake, resulting in significant improvement in feed efficiency. Carcass weight was increased 2–8 kg, and carcasses contained less fat and more muscle and protein on a relative basis. Cattle fed Optaflexx contained approximately 10 kg more lean muscle than did control animals consuming the same amount of feed. Meat palatability characteristics including taste, texture and juiciness, and quality grade of the beef from cattle fed Optaflexx were not altered at any approved dosage of feeding. Summary data suggest a slight decrease in tenderness, measured as trained sensory panel ratings and mechanical Warner-Bratzler shear force in cooked strip loin steaks, when the highest dosage (300 mg per head per d) was fed (Schroeder et al. 2003). These differences may be undetectable by consumers because the increase in shear force (+0.4 kg) was below the range in change that normally can be detected by consumers (0.45–1.8 kg).

Zilpaterol (Zilmax) also improves growth performance, carcass weight, and the yield of muscle from the carcass when fed to finishing cattle, but it has not been approved by the FDA. Zilpaterol had no negative effects on meat quality when fed for 15 or 30 d, but feeding it for 45 d until 48 hours (h) before harvest resulted in lower sensory tenderness and juiciness ratings for the longissimus muscle, and the shear force of the muscle also was negatively affected (Strydom et al. 1999). Therefore, time fed may have to be restricted to fewer than 45 d in certain instances where meat quality is important.

Beta-agonist Mechanism of Action

Beta-agonists act directly through ß-adrenergic receptors on skeletal muscle and adipose cell membranes and generate signals that control metabolic activities in the cells. When ractopamine or other ß-agonists bind to

the ß-adrenergic receptors on fat cells, biochemical signals are initiated, activating several enzymes in the pathways that lead to decreased rates of *lipogenesis* (lipid synthesis and storage) and to increased *lipolysis* (lipid mobilization in the cell) (Dunshea 1993; Mersmann 1989; Mills and Liu 1990). The rate of fat accumulation or growth in the animal slows, resulting in a leaner animal. The magnitude of these changes is influenced by the dose (amount) and the length of time the ß-agonist is consumed, the type of ß-agonist, and the target species (Beermann 1993; Mersmann 1998; Moody, Hancock, and Anderson 2002).

Skeletal muscle cells also contain ß-adrenergic receptors. Interaction of a ß-agonist with the receptor stimulates similar signaling pathways as in fat cells, altering muscle metabolism in a dose-dependent manner (Byrem, Beermann, and Robinson 1996). Direct infusion of the ß-agonist cimaterol, a ß-agonist that has not been approved as a metabolic modifier, into the hind limb of growing steers increases the rate of amino acid extraction from the blood and results in increased rates of muscle protein synthesis and muscle growth (Byrem, Beermann, and Robinson 1998), independent of any systemic endocrine changes. Uncertainty remains regarding direct effects on protein turnover rates (see review by Beermann 2002). The muscle growth enhancement results from *hypertrophy* (an increase in cell size) without any increase in cell number. The total number of muscle fibers in a muscle generally is set at birth in most domestic animal species. The changes that occur in skeletal muscle and adipose tissue are progressive over short periods of time, but they are not sustained over long periods because desensitization of receptors on target tissues occurs. For example, there is a marked down-regulation in adipose tissue of swine within 4 d after the commencement of feeding of Paylean (Dunshea and King 1995). Therefore, the recommended time of feeding is near the end of the finishing period. Longer feeding time has little or no effect on muscle or adipose tissue growth and would result in markedly decreased economic benefit.

Less energy per weight is required to grow muscle than to grow adipose tissue. Use of feed for growth in animals fed ß-agonists is more efficient overall. The ß-agonists stimulate muscle growth and decrease the rate of nutrient use for adipose tissue growth, resulting in less feed required to produce an animal of the same weight. Less animal waste is produced, decreasing environmental impact when ß-agonists are fed to meat-producing animals.

Safety of Feeding ß-agonists to Meat Animals

Extensive testing using stringent criteria to address the safety of feed additives and animal health products is mandated by the FDA before a product is allowed to be marketed for animals intended for food. Tests include chronic toxicity, mutagenicity, lifetime carcinogenicity, and effects on reproduction over two generations in animal model systems. The food safety for humans consuming foods of animal origin when feed additives are used also is tested. The safety evaluation of ractopamine hydrochloride—the active ingredient in Paylean and Optaflexx—included extensive tests in both laboratory animals and meat animals to establish safety of the approved dosages and conditions under which Paylean and Optaflexx are produced and used.

In 1989 the EU banned all ß-agonists for use in meat animals, but no full scientific evaluation of ß-agonists was conducted to support the ban, particularly for those approved for use elsewhere (APVMA 2003). Illegal and unsafe use of ß-agonists was, and continues to be, a problem in many parts of the world, and this practice may have contributed to the EU ban.

In this context, an important distinction must be made between ractopamine and other ß-agonists. Ractopamine is what might be described as a recent-generation ß-agonist specifically designed to meet the desired properties of an in-feed ingredient. These properties include rapid clearance from the body, targeting of specific tissues such as muscle and fat, no residues at slaughter, and no conversion of the compound to other active compounds. By contrast, early-generation ß-agonists such as cimaterol, salbutamol, and clenbuterol were designed to act like pharmaceutical medicines used in the treatment of respiratory and other diseases, and the desired properties of such medicines are different from those required for an in-feed ingredient for finisher animals. For example, these compounds have a longer retention time in the body; act on a number of tissues rather than targeting specific ones; and result in residues in the body, particularly in the liver and kidney. Persons eating organs containing significant residues of an illegal ß-agonist risk developing symptoms of ß-agonist toxicity (heart fibrillations and bronchial spasms). In addition, certain ß-agonists used illegally (e.g., clenbuterol) also are converted to more active or toxic compounds, which are retained in tissues. Ractopamine is not converted to more active or toxic compounds, and hence it has been approved for use in meat animals.

Ractopamine also has been evaluated for possible effects on animal welfare. Animal health, behavior, and well-being were evaluated extensively at dosages at least ten times higher than dosages approved for use in meat animals. There were subtle changes in certain behaviors in some pigs fed 10 ppm ractopamine hydrochloride, making them more difficult to handle and potentially more susceptible to handling and transport stress (Marchant-Forde et al. 2003). No effects were noted, however, in most studies.

Somatotropin (Growth Hormone)

Somatotropin is a naturally occurring protein hormone produced by the anterior pituitary gland and secreted into the blood circulatory system. It differs slightly in structure among animal species, and so a degree of species specificity exists. For example, neither bST nor pST is active in humans. Somatotropin has several important roles in the regulation of development and growth of skeletal muscle, bone, adipose tissue, and the liver in growing animals. It plays an integral role in the coordination of lipid, protein, and mineral metabolism in livestock and other mammalian species. Elevation of ST in the circulation redirects nutrients toward increased muscle and bone growth and decreased adipose tissue growth in meat animals (Etherton and Bauman 1998). It also enhances milk production in lactating dairy cows (Bauman 1999; Bauman and Vernon 1993). Efficiency of total body weight gain during growth and of milk production also is improved, resulting in decreased amounts of nutrients excreted per unit of meat and milk produced.

Bovine ST and pST initially were produced by extraction and purification from pituitary glands of cattle and pigs. The amounts available using this technology were insufficient to allow scientists to use these technologies for investigations in large animals. Recombinant DNA technology was used in the early 1980s to produce the amounts needed for scientific investigations in food-producing animals and is used today to accommodate commercial application. In 1994, the FDA approved Posilac, the prolonged-release bST formulation produced by Monsanto (St. Louis, Missouri). Its use has increased gradually to approximately one-fourth of the dairy cows in the United States. Field performance has demonstrated that increases in milk yield, milk fat, and milk protein were consistent each year in more than 350 herds and more than 800,000 cows administered bST during the first 4 yr after approval (Bauman et al. 1999). Porcine ST is not approved for use in the United States, but it is approved for use in 14 other countries (Dunshea et al. 2002).

Efficacy of Somatotropin in Lactating Dairy Cows

Early studies in which pituitary-derived bST was administered for 10–12 weeks (wk) resulted in up to 40% increases in milk production without adverse effects (Brumby and Hancock 1955; Machlin 1973). The initial limited supply of bST constrained treatment to relatively few animals in the studies designed to enhance understanding of the biological effects of bST; therefore, progress was slow. The more efficient production of recombinant bST allowed more rigorous evaluation of the mechanism(s) of action and temporal pattern of increased milk yield as well as investigation of factors influencing the magnitude and longevity of increased milk yield response. Results from early short-term studies (Bauman et al. 1982), as well as from long-term (188 d) studies (Bauman et al. 1985), using recombinant-produced bST demonstrated impressive increases in milk yield and production efficiency. The availability of bST increased rapidly once new recombinant technology was improved thereafter, and many studies were conducted around the world to evaluate the potential for commercial application in the dairy industry.

Studies using ST demonstrated and evaluated many important concepts and concerns regarding effects on dairy cattle metabolism, health and well-being, nutritional requirements, milk composition and quality, and product safety from animal and human perspectives. Findings include the following:

1. Increases in milk production occur quickly after starting bST administration, and feed intake increases over the first few weeks to accommodate the increased demand for nutrients used for milk synthesis and secretion (Peel and Bauman 1987). Inadequate provision of nutrients will lessen the response to bST, but special diets are not needed. Good management to provide adequate amounts and availability of normal diets will facilitate the full response to bST administration (NRC 1994).
2. The composition of milk and the manufacturing characteristics of milk are not altered with bST administration (Laurent et al. 1992; Van den Berg 1991). Milk composition differences associated with breed, genetics, stage of lactation, diet, environment, and season are identical whether bST is administered or not. The amount of insulin-like growth factor-1 (IGF-1) in milk increases modestly after

bST supplementation but does not exceed normal concentrations, which vary during lactation.

3. The amount of energy expended by the cow for maintenance requirements and the partial efficiency of milk synthesis are not altered by bST (Kirchgessner et al. 1991; Tyrrell et al. 1988). The latter is true because the metabolic pathways of milk synthesis and secretion do not differ when bST is used. Cellular rates of milk synthesis are increased and the secretory cells persist longer with bST administration (Knight, Fowler, and Wilde 1990). The lack of change in energy requirements for normal body functions and the longer persistence of lactation indicate that general well-being of the animal is not affected adversely.
4. Larger proportions of nutrients consumed are used for milk production, and smaller proportions of nutrients are excreted in the urine and feces, decreasing the amount of waste per unit of milk produced (Johnson, Ward, and Torrent 1992). This improved efficiency in use of absorbed nutrients results from the chronic coordination of physiological processes and tissue metabolism. These changes redirect nutrients toward use by the mammary gland by altering carbohydrate, protein, lipid, and mineral metabolism in other tissues such as the liver, skeletal, muscle, and adipose tissue without causing metabolic disorders such as diabetes, *ketosis*, or decreased cow productivity (Bauman 1999).
5. Normal reproductive function, fetal development during pregnancy, and health status of the cow and calf are not affected by bST administration. No increase in clinical or subclinical disease to the fetus of any kind is caused by bST. The FDA, medical associations, and scientific societies conclude that use of bST poses no health or safety concerns for consumers (Hartnell 1995).

Safety of Somatotropin

Determination of the human food safety of ST included extensive tests in laboratory animals and in dairy and meat animals to establish the safety of both bST and pST. Somatotropin occurs naturally in milk and meat, and the concentrations are not increased during bST treatment. Even if bST or pST treatment increased the concentration of ST in milk or meat, however, this probably would pose no threat to humans, because ST is a protein that has a species-specific structure. Moreover, both bST and pST are inactive in humans, even when administered by injection (Kievits et al. 1988). Studies with rats orally dosed with more than 100 times the daily dose (per kg live weight) recommended for use in farm animals demonstrated that bST is digested into either single amino acids or small *peptides*, none of which has any ST-like activity.

Efficacy of Somatotropin in Growing Pigs and Ruminants

Subcutaneous administration of ST is required for bioactivity because oral administration would result in digestion of the hormone in the gut, similar to what occurs with all ingested proteins. Daily subcutaneous administration allows an animal to absorb the hormone over time (1–6 h) and leads to responses considered representative of true genetic potential for muscle growth. Daily administration of pST increases average daily gain and feed conversion efficiency and improves carcass composition in a dose-dependent manner (Campbell et al. 1988, 1989, 1991; Dunshea et al. 2002; Etherton et al. 1987). Total carcass muscle mass at the same live weight was increased by 28% with a low pST dose of 50 micrograms (μg)/kg live weight and by 38% with a high dose of 200 μg pST/kg live weight (Krick et al. 1992). Dose-dependent decreases in lipid concentration in muscle and amount of adipose tissue were observed throughout the carcass (Thiel et al. 1993). These studies provided a comprehensive characterization of responses to pST when pigs were fed an adequate diet. Smaller responses were observed if the provision of nutrients, particularly protein, was inadequate. Because pST decreases both fat deposition and feed intake, the correct nutrient specifications of the diet are key to optimizing the response.

There is little effect of ST on nutrient digestibility. Effects result from an increase in the efficiency of use of dietary protein. In some cases, an increase in dietary protein requirement may occur to support increased protein deposition. Administration of pST has little or no effect on dietary protein requirements in grower pigs (30–60 kg live weight), but there is an improvement in the efficiency of amino acid usage (Campbell et al. 1991). Porcine ST has little effect on the efficiency of dietary protein use in finisher pigs (60–120 kg), and there is an increase in the protein requirement commensurate with the increase in protein deposition (Campbell et al. 1991; Dunshea 1994). Failure to increase dietary protein will decrease the effects of pST on stimulating protein and lean tissue deposition.

Although the amounts of dietary protein and energy intake do influence protein gain responses, fat gain is decreased at every amount of dietary protein or energy intake in pigs administered pST. At all amounts of energy intake, protein gain is higher and fat and total energy gains are lower in pigs treated with pST. The increased protein mass and protein synthesis rate result in an increase in maintenance energy requirement. The increased maintenance requirement in combination with the decreased feed intake often may limit the response to pST when dietary intake is inadequate to support the muscle growth potential (Dunshea 1994).

Protein deposition in growing ruminants often is limited by dietary energy consumption, which may explain why ruminants treated with ST do not exhibit decreased feed intake. Lipid deposition also is decreased and the energy spared from the decrease in lipid synthesis is partitioned toward protein deposition (or milk secretion in lactation). Therefore, if the full benefits of *exogenous* ST are to be achieved, nutrient intake needs to be maximized regardless of species or physiological state.

The amount and quality of dietary protein also may limit the effect of ST on protein deposition in the ruminant. This idea is supported by the observation that providing additional high-quality protein in the form of casein infused into the *abomasum* (true stomach) increases the response to bST (Beermann et al. 1991; Houseknecht et al. 1992).

Dose-dependent increases in absolute body mass and percentage of muscle in carcasses of pigs, lambs, and cattle provide unequivocal evidence for the importance of ST influence on skeletal muscle growth (NRC 1994). The increase in skeletal growth is occasionally associated with certain subtle changes in meat quality. For example, subjective fat marbling scores and intramuscular fat are consistently decreased by pST. Slight or no effects of pST on objective and subjective measures of meat tenderness, appearance, and shelf life have been reported (Dunshea 1994).

Somatotropin Mechanisms of Action

The physiological and metabolic effects of ST are influenced by physiological state, but in all instances ST coordinates metabolism to partition nutrients toward lean tissue and bone (during growth) or toward milk synthesis (during lactation). Many effects of ST are direct and mediated through changing responses to *homeostatic* hormones such as insulin or catecholamines. Other effects are indirect and thought to be mediated by the IGF system.

It is well established that ST increases protein deposition and milk protein synthesis in growing and lactating animals, respectively, but the precise mechanisms and extent to which effects on protein metabolism are direct or indirect via the IGF system remain subjects of active investigation. Most studies suggest that in growing animals the increase in protein deposition results primarily from an increase in protein synthesis with little effect on protein degradation. The increase in protein synthesis also is associated with a decrease in amino acid oxidation (used as an energy source), allowing a greater proportion of absorbed amino acids to be used for protein accretion.

Treatment of lactating cows with bST results in an increased synthesis of all milk constituents, consistent with the increase in milk yield. The mechanism involves both an increase in the synthetic capacity and an improved maintenance of mammary epithelial cells. Coordinated increases in mammary blood flow and mammary uptake of nutrients also occur. The increased milk synthesis is supported by a series of orchestrated changes in other body tissues that ensure that the mammary gland is supplied with the quantity and pattern of nutrients needed to support milk synthesis. These coordinated adaptations involve most tissues in the cow's body.

Lipid synthesis in adipose tissue from growing pigs treated with pST is decreased by up to 85% (Dunshea et al. 1992). The ability of insulin to stimulate lipid synthesis is decreased similarly, mainly the result of a decreased sensitivity to insulin. Administration of pST decreases rates of glucose clearance from the blood in response to an insulin or glucose challenge, and there is an augmented plasma insulin response to increased glucose absorption after a meal (Wray-Cahen et al. 1991). It has been suggested that the insulin resistance and resultant decreased adipose tissue lipogenesis and glucose oxidation largely are responsible for the decrease in feed intake observed with pST treatment. Treatment with somatotropin also causes lipolysis, or an increase in lipid breakdown, in response to adrenergic stimulation in pigs and cattle.

Developing Metabolic Modifier Technologies

Additional compounds currently are being investigated for efficacy and safety in meat-producing animals.

These compounds include the feed additives betaine and chromium picinolate, and a vaccine (Improvac) that increases growth rate and decreases boar taint common in pork from pigs raised to market weight as intact males (Dunshea et al. 2001). Plasmid vector administration of growth-hormone-releasing hormone in muscle of animals shows promise as a new technology for achieving effects similar to those observed with ST administration (Draghia-Akli et al. 2003).

Conclusion

Scientific research directed toward understanding the regulation of nutrient use in agricultural animals has led to commercial development, FDA approval, and the use of metabolic modifiers. The three classes of metabolic modifiers in use include estrogenic and androgenic anabolic implants for growing and finishing beef cattle; ß-adrenergic agonists fed to finishing beef cattle and swine; and somatotropin (growth hormone), which is administered to lactating dairy cattle. In some countries somatotropin also is approved for use in swine. These compounds modify animal metabolism in specific, targeted ways to increase weight gain and the amount of meat or milk produced per unit of feed consumed, thus improving the overall productive efficiency of meat or milk production. Rigorous evaluation required for approval by the FDA ensures safety in all aspects of their use: animal well-being, farm worker safety, and wholesomeness and safety of the food products derived from the animals. The ultimate benefits of both the currently approved metabolic modifiers and the successful development efforts under investigation are the enhanced sustainability and the profitability of livestock production, and decreased return of nutrients to the environment. These benefits are shared by producers, processors, and consumers. Producers benefit because of improved production efficiencies; meat and milk processors because of increased lean meat or milk yield; and consumers because of healthier, less expensive products and the assurance that stringent animal and human safety requirements have been met.

Glossary

Abomasum. True stomach; fourth compartment of the ruminant stomach that has a true digestive function.

Adipose tissue. Connective tissue in which lipid is stored and cells are distended by accumulation of lipid.

Anabolic. Concerning the constructive part of metabolism.

Androgenic. Relating to a male sex hormone.

Beta-adrenergic agonist. Phenethanolamine chemical compounds similar to epinephrine that elicit physiological responses through specific hormone receptors located in cell membranes.

Estrogenic. Of, relating to, caused by, or being an estrogen.

Exogenous. An agent or compound that originates from outside the organism or system.

Homeostatic. Physiological process by which the internal systems of the body are maintained at equilibrium despite variations in external conditions.

Hypertrophy. Increase in cell size in a tissue or organ.

Immunomodulation. Process by which a substance affects the functioning of the immune system.

Implant. Device or substance placed under the skin (in animals, especially in the ear) that releases hormones or drugs over a sustained period.

Ketosis. A buildup of ketone bodies in the circulation, often occurring during periods of fat mobilization and production of ketone bodies from fatty acids.

Lipogenesis. Lipid synthesis and storage.

Lipolysis. Lipid mobilization or breakdown.

Peptide. Two or more amino acids joined by a bond called a "peptide bond." Often used to describe a small protein.

Plasmid vector administration. Administration of DNA originating from a plasmid into which another DNA fragment has been incorporated. The introduced DNA then is replicated in the new host.

Protein turnover. Protein degradation and replacement that occurs naturally in cells.

Somatotropin. Growth hormone.

Subcutaneous. Being, living, used, or made under the skin.

Synthetic analogues. Manufactured chemical compounds that share similar structure and function with naturally occurring compounds.

Withdrawal. Removal or cessation of administration.

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Literature Cited

Australian Pesticides and Veterinary Medicines Authority (APVMA). 2003. A review to update Australia's position on the human safety of residues of hormone growth promotants (HGPs) used in cattle. Department of Health and Ageing, <http://www.apvma.gov.au/publications/review_HGP.doc> (5 May 2004)

Bartle, S. J., R. L. Preston, R. E. Brown, and R. J. Grant. 1992. Trenbolone acetate/estradiol combinations in feedlot steers: Dose-response and implant carrier effects. *J Anim Sci* 70:1326–1332.

Bauman, D. E. 1999. Bovine somatotropin and lactation: From basic science to commercial application. *Dom Anim Endo* 17:101–116.

Bauman, D. E. and R. G. Vernon. 1993. Effects of exogenous bovine somatotropin on lactation. *Annu Rev Nutr* 13:437–461.

Bauman, D. E., M. J. DeGeeter, C. J. Peel, G. M. Lanza, R. C. Gorewit, and R. W. Hammond. 1982. Effect of recombinantly derived bovine growth hormone (bGH) on lactational performance of high yielding dairy cows. *J Dairy Sci* 65(Suppl 1):121.

Bauman, D. E., P. J. Eppard, M. J. DeGeeter, and G. M. Lanza. 1985. Responses of high-producing dairy cows to long-term treatment with pituitary somatotropin and recombinant somatotropin. *J Dairy Sci* 68:1352-1362.

Bauman, D. E., R. W. Everett, W. Weiland, and R. J. Collier. 1999. Production responses to bovine somatotropin in northeast dairy herds. *J Dairy Sci* 82:2574–2581.

Beermann, D. H. 1993. ß-adrenergic agonists and growth. Pp. 345–366. In M. P. Schriebman, C. G. Scanes, and P. K. T Pang (eds.). *The Endocrinology of Growth, Development and Metabolism in Vertebrates*. Academic Press, San Diego, California.

Beermann, D. H. 2002. ß-adrenergic agonist receptor modulation of skeletal muscle growth. *J Anim Sci* 80 (E. Suppl.1): 18–23.

Beermann, D. H., T. F. Robinson, T. M. Byrem, D. E. Hogue, A. W. Bell, and C. L. McLaughlin. 1991. Abomasal casein infusion and exogenous somatotropin enhance nitrogen utilization by growing lambs. *J Nutr* 121:2020–2028.

Brumby, P. J. and J. Hancock. 1955. The galactopoetic role of growth hormone in dairy cattle. *NZ J Sci Technol* 36:417–436.

Byrem, T. M., D. H. Beermann, and T. F. Robinson. 1996. Characterization of dose-dependent metabolic responses to close arterial infusion of cimaterol in the hindlimb of steers. *J Anim Sci* 74:2907–2916.

Byrem, T. M., D. H. Beermann, and T. F. Robinson. 1998. The ß-agonist cimaterol directly enhances chronic protein accretion in skeletal muscle. *J Anim Sci* 76:988–998.

Campbell, R. G., N. C. Steele, T. J. Caperna, J. P. McMurtry, M. B. Solomon, and A. D. Mitchell. 1988. Interrelationships between energy intake and exogenous growth hormone administration on the performance, body composition and protein and energy metabolism of growing pigs weighing 22 to 55 kg body weight. *J Anim Sci* 66:1643–1655.

Campbell, R. G., N. C. Steele, T. J. Caperna, J. P. McMurtry, M. B. Solomon, and A. D. Mitchell. 1989. Interrelationships between sex and exogenous growth hormone administration and performance, body composition and protein and fat accretion of growing pigs. *J Anim Sci* 67:177–186.

Campbell, R. G., R. J. Johnson, M. R. Taverner, and R. H. King. 1991. Interrelationships between exogenous porcine somatotropin (pST) administration and dietary protein and energy intake on protein deposition capacity and energy metabolism of pigs. *J Anim Sci* 69:1522–1531.

Draghia-Akli, R., K. M. Ellis, L. A. Hill, P. B. Malone, and M. L. Fiorotto. 2003. High-efficiency growth hormone-releasing hormone plasmid vector administration into skeletal muscle mediated by electroporation in pigs. *FASEB J* 17:526–528.

Dunshea, F. R. 1993. Effects of metabolism modifiers on lipid metabolism in the pig. *J Anim Sci* 71:1966–1977.

Dunshea, F. R. 1994. Nutrient requirements of pigs treated with metabolic modifiers. *Proc Nutr Soc of Aust* 18:103–114.

Dunshea, F. R. and N. J. Gannon. 1995. Nutritional and other factors affecting efficacy of ß-agonists for pigs. Pp. 46–52. In J. B. Rowe and J. V. Nolan (eds.). *Recent Advances in Animal Nutrition in Australia*. University of New England, Armadale, Australia.

Dunshea, F. R. and R. H. King. 1995. Responses to homeostatic signals in ractopamine-treated pigs. *Brit J Nutr* 73:809–818.

Dunshea, F. R., D. M. Harris, D. E. Bauman, R. D. Boyd, and A. W. Bell. 1992. Effect of porcine somatotropin on in vivo glucose kinetics and lipogenesis in the growing pig. *J Anim Sci* 70:141–151.

Dunshea, F. R., C. Colantoni, K. Howard, P. Jackson, K. A. Long, S. Lopaticki, E. A. Nugent, J. A. Simons, J. Walker, and D. P. Hennessy. 2001. Vaccination of entire boars with Improvac® eliminates boar taint and increases growth performance. *J Anim Sci* 79:2524–2535.

Dunshea, F. R., M. L. Cox, M. R. Borg, M. N. Sillence, and D. R.

Harris. 2002. Porcine somatotropin (pST) administered using a commercial delivery system improves growth performance of rapidly-growing, group-housed finisher pigs. *Aust J Agri Res* 53:287–293.

Elanco Technical Bulletin AI8941. 2003. Utilizing Optaflexx to maximize your investment. Elanco Animal Health, Greenfield, Indiana.

Etherton, T. D. and D. E. Bauman. 1998. The biology of somatotropin in growth and lactation of domestic animals. *Physiol Rev* 78:745–761.

Etherton, T. D., J. P. Wiggins, C. M. Evock, C. S. Chung, J. F. Rebhun, P. E. Walton, and N. C. Steele. 1987. Stimulation of pig growth and performance by porcine growth hormone: Determination of the dose-response relationship. *J Anim Sci* 64:433–443.

Guiroy, P. J., L. O. Tedeschi, D. G. Fox, and J. P. Hutcheson. 2002. The effects of implant strategy on finished body weight of beef cattle. *J Anim Sci* 80:1791–1800.

Hancock, D. L., J. F. Wagner, J. F., and D. B. Anderson. 1991. Effects of estrogens and androgens on animal growth. Pp. 255–297. In A. M. Pearson and T. R. Dutson (eds.). *Growth Regulation in Farm Animals. Advances in Meat Research*, Vol. 7. Elsevier Applied Science, Essex, United Kingdom.

Hartnell, G. F. 1995. Bovine somatotropin: Production, management and United States experience. Pp. 189–203. In M. Ivan (ed.). *Animal Science Research and Development: Moving Toward a New Century*. Center for Food and Animal Research, Agriculture and Agri-Food, Ottawa, Ontario, Canada.

Houseknecht, K. L., D. E. Bauman, D. E. Fox, and D. F. Smith. 1992. Abomasal infusion of casein enhances nitrogen retention in somatotropin-treated steers. *J Nutr* 122:1717–1725.

Johnson, B. A, P. T. Anderson, J. C. Meiske, and W. R. Dayton. 1996. Effect of a combined trenbolone acetate and estradiol implant on feedlot performance, carcass characteristics and carcass composition of feedlot steers. *J Anim Sci* 74:363–371.

Johnson, D. E., G. M. Ward, and J. Torrent. 1992. The environmental impact of bovine somatotropin use in dairy cattle. *J Environ Qual* 21:157–162.

Kievits, J. M., H. C. van Dam, H. W. Hessel, and A. Brand. 1988. Somatotropin: Structure, (bio)synthesis and species specificity. *Tijdschr Diergeneesk* 113:791–800.

Kirchgessner, M., W. Windisch, W. Schwab, and H. L. Muller. 1991. Energy metabolism of lactating dairy cows treated with prolonged-release bovine somatotropin or energy deficiency. *J Dairy Sci* 74(Suppl 2):35–43.

Knight, C. H., P. A. Fowler, and C. J. Wilde. 1990. Galactopoietic and mammogenic effects of long-term treatment with bovine growth hormone and thrice daily milking in goats. *J Endocrinol* 127:129–138.

Krick, B. J., K. R. Roneker, R. D. Boyd, D. H. Beermann, P. J. David, and D. J. Meisinger. 1992. Influence of genotype and sex on the response of growing pigs to recombinant porcine somatotropin. *J Anim Sci* 70:3024–3034.

Kuiper, H. A., M. Y. Noordam, M. M. van Dooren-Flipsen, R. Schilt, and A. H. Roos. 1998. Illegal use of beta-adrenergic agonists: European Community. *J Anim Sci* 76:195–207.

Laurent, F., B. Vignon, D. Coomans, J. Wilkinson, and A. Bonnel. 1992. Influence of bovine somatotropin on the composition and manufacturing properties of milk. *J Dairy Sci* 75:2226–2234.

Machlin, L. 1973. Effect of growth hormone on milk production and feed utilization in dairy cows. *J Dairy Sci* 56:575–580.

Marchant-Forde, J. N., D. C. Lay, E. A. Pajor, B. T. Richert, and A. P. Schinckel. 2003. The effects of ractopamine on the behaviour and physiology of finishing pigs. *J Anim Sci* 81:416–422.

Mersmann, H. J. 1989. Inhibition of porcine adipose tissue lipogenesis by ß-adrenergic agonists. *Comp Biochem Physiol* 94C:619–623.

Mersmann, H. J. 1998. Overview of effects of ß-adrenergic receptor agonists on animal growth including mechanisms of action. *J Anim Sci* 76:160–172.

Mills, S. E. and C. Y. Liu. 1990. Sensitivity of lipolysis and lipogenesis to dibutyryl-cAMP and ß-adrenergic agonists in swine adipocytes in vitro. *J Anim Sci* 68:1017–1023.

Moody, D. E., D. L. Hancock, and D. B. Anderson. 2002. Phenethanoloamine repartitioning agents. Pp. 65–96. In J. P. F. D'Mello (ed.). *Farm Animal Metabolism and Nutrition*. CAB International, New York.

National Research Council (NRC). 1994. *Metabolic Modifiers: Effects on the Nutrient Requirements of Food-producing Animals*. National Academies Press, Washington, D.C.

National Research Council (NRC). 1996. *Nutrient Requirements of Beef Cattle*. 7th rev. ed. National Academies Press, Washington, D.C.

National Research Council (NRC). 2000. *Nutrient Requirements of Beef Cattle*. 7th rev. ed., update 2000. National Academies Press, Washington, D.C.

Nichols, W. T., M. L. Galyean, D. U. Thomson, and J. P. Hutcheson. 2002. Effects of steroid implants on the tenderness of beef. *Prof Anim Sci* 18:202–210.

Peel, C. J. and D. E. Bauman. 1987. Somatotropin and lactation. *J Dairy Sci* 70:474–486.

Perry, T. C., D. G. Fox, and D. H. Beermann. 1991. Effect of an implant of trenbolone acetate and estradiol on growth, feed efficiency, and carcass composition of Holstein and beef steers. *J Anim Sci* 69:4696–4702.

Schroeder, A. L., D. M. Polser, S. B. Laudert, and G. J. Vogel. 2003. Effects of Optaflexx on sensory properties of beef. "Optaflexx Exchanges" Elanco Technical Bulletin AI9253, Elanco Animal Health, Greenfield, Indiana.

Strydom, P. E., E. A. Osler, K-J Leeuw, and E. Nel. 1999. The effect of supplementation period of a beta-agonist (Zilpaterol), electrical stimulation and ageing period on meat quality characteristics. *Proc 45th Intl Congr of Meat Sci and Technol* 2:58–59, Yokohama, Japan.

Thiel, L. F., D. H. Beermann, B. J. Krick, and R. D. Boyd. 1993. Dose-dependent effects of exogenous porcine somatotropin on the yield, distribution, and proximate composition of carcass tissues in growing pigs. *J Anim Sci* 71:827–835.

Tyrrell, H. F., A. C. G. Brown, P. J. Reynolds, G. L. Haaland, D. E. Bauman, C. J. Peel, and W. D. Steinhour. 1988. Effect of bovine somatotropin on metabolism of lactating dairy cows: Energy and nitrogen utilization as determined by respiration calorimetry. *J Nutr* 118:1024–1030.

Van den Berg, G. A. 1991. A review of quality and processing suitability of milk from cows treated with bovine somatotropin. *J Dairy Sci* 74(Suppl 2):2–11.

Wray-Cahen, D., D. A. Ross, D. E. Bauman, and R. D. Boyd. 1991. Metabolic effects of porcine somatotropin: Nitrogen and energy balance and characterization of the temporal pattern of blood metabolites and hormones. *J Anim Sci* 69:1503–1514.

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