Mechanisms Responsible for Partitioning Tissue Growth in Meat Animals

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Introduction

Aspects of Livestock Production Efficiency

The depressed market prices for meat animals experienced over the last several months highlight the importance of production efficiency in determining the economic survival or demise of animal agriculture. Feed grains, although abundantly available, represent the largest single cost factor in meat animal production. Therefore, reducing the feed required per unit of product can greatly improve cost effectiveness. Many of the growth promotants (estrogens, androgens, rumen modifiers) and combinations of these do reduce feed intake and increase growth rate.

Production efficiency of meat animals is also dramatically limited by the ever-present biological phenomenon of allometric growth. We define allometric growth as the relative growth of each of the major tissues (bone, skeletal muscle and adipose) in relation to total body weight or carcass weight. Allometric growth in meat animals results in accelerated adipose accumulation during continued linear increase in muscle mass and a declining rate of bone growth as the animal approaches market weight. These tissue growth patterns markedly influence growth efficiency because utilization of metabolizable energy is influenced by composition of the gain. Protein gain is energetically less efficient than lipid gain as a result of the costs of protein turnover as well as nutrient and ion transport associated with protein synthesis and maintenance (Garrett and Johnson, 1983). However, muscle growth or weight increase is probably more efficient than fat accretion because the water content of muscle is generally five to ten times greater. Therefore, partitioning of tissue growth toward increased muscle weight gain and decreased fat accretion should also markedly improve growth efficiency. Altering tissue growth will either require or be directed by changes in nutrient availability to skeletal muscle and adipose tissue.

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Strategies Available for Altering Partitioning of Tissue Growth

Various strategies are available for altering the normal partitioning of tissue growth in meat animals. These are listed below without regard to relative importance, degree of response or limitations.

1. Invoke genetic selection for single or multiple traits which are easily and accurately measured in the live animal or carcass.
2. Use a large mature size male (breed) in a terminal-cross breeding system for market animal production.
3. Use restricted feeding in nonruminants to reduce energy intake or alter the calorie-protein ratio when adding fat to the diet.
4. Capitalize on natural sex differences in tissue growth patterns (i.e., intact males vs. females).
5. Alter cellularity or cellular characteristics of skeletal muscle or adipose tissue.
6. Alter nutrient partitioning to coordinate a redirection of nutrient use away from adipose tissue accretion toward greater skeletal muscle growth. This effect is termed "repartitioning."

The confirmation of the repartitioning effects of somatotropin (growth hormone) and the recently-discovered synthetic repartitioning beta-adrenergic agonists clenbuterol and cimaterol have established new vistas for repartitioning tissue growth.

It is essential that we as animal scientists seek to fully understand the mechanisms involved in the complex biological processes being altered by these repartitioning agents. With this knowledge, we can systematically continue to improve meat animal growth.

Many of the results from recent studies with repartitioning agents have not as yet been published. Therefore, information is presented which characterizes and compares the tissue repartitioning response observed with somatotropin and the beta-adrenergic agonists. Data is subsequently presented which begins to define control points and mechanisms involved in bringing about these repartitioning effects. Data is first presented which addresses the cellular aspects of the altered tissue growth patterns. Second, plasma meta-

bolic hormone profiles, metabolite levels, and metabolite turnover rates are presented to contrast changes seen with somatotropin and the adrenergic agonists. Last, other physiological changes which further enlighten us as to the mechanisms involved are also presented.

Effects of Somatotropin on Partitioning Tissue Growth

Until very recently, studies assessing the tissue repartitioning effects of somatotropin have yielded somewhat inconsistent results (Olsen, 1984). Although Machlin (1972) detected an 11% increase in carcass protein and a 35% decrease in carcass fat in swine given daily injections of porcine somatotropin, earlier studies (Turman and Andrews, 1955; Henricson and Ullberg, 1960) failed to document a similar response. The same is true for sheep. Wagner and Veenhuizen (1978) observed a marked increase (25%) in carcass protein and a 37% decrease in fat in 40-kg wethers treated for 98 to 112 days, but Muir et al. (1983) observed a much smaller response in 28-kg wethers treated for 56 days. Neither somatotropin-induced changes in carcass composition nor direct measures of tissue growth response in beef cattle have been reported in the literature.

Several studies conducted by Etherton and co-workers strongly support the effectiveness of somatotropin in repartitioning tissue growth in swine (see Table 1). Chung and Etherton (1985) observed a 6.2% increase ($p<.01$) in carcass muscle mass in 32-kg barrows treated with porcine somatotropin (22μg/kg body weight/day) for 30 days, while carcass adipose tissue was not reduced. In a more recent study, (Etherton et al., 1985) 50-kg barrows received 0 or 30μg/kg/d porcine somatotropin or human pancreatic somatotropin-releasing factor (hpGRF) for 30 days. The percentage of carcass lipid was reduced 18% by somatotropin ($p<.05$) and 13% with hpGRF ($p<.05$). Muscle mass was increased by 35% with somatotropin, but not significantly altered with hpGRF. In a third experiment, muscle mass was increased and carcass fat decreased in a linear fashion with increasing somatotropin dose (0, 10, 30 and 70μg pGH/kg) in 43-kg barrows treated for 35 days (Rebhun et al., 1985). Average daily gain was increased by approximately 10% ($p<.05$) with pGH in all three experiments and feed efficiency was also improved between 4% and 21%.

Similar data are now available which demonstrate somatotropin-induced repartitioning of tissue growth in young growing cattle (Sejrsen and Bauman, unpublished data). Daily injection of bovine somatotropin (20 IU/d; 1.3 IU/mg) given nine pairs of monozygous twin dairy heifers (8 months of age; 179-kg body weight) for 100 to 112 days resulted in greater percentage carcass muscle (p .01) and less percentage carcass fat ($p<.001$; Table 2). Percentage of carcass in the loin and round and percentage of muscle in loin and round were also greater with somatotropin administration, demonstrating a differential shift in tissue growth patterns by anatomical location. Taste panel results indicated no effect of somatotropin on eating quality of the longissimus muscle. Intramuscular fat in the longissimus was less with somatotropin treatment, but protein content and color were not different. Somatotropin improved ADG by about 10 percent and markedly improved feed efficiency.

Effects of Selected Beta-Adrenergic Agonists on Repartitioning Tissue Growth

Last year at these meetings, Catherine Ricks (American Cyanamid Company) presented data which demonstrated the tissue repartitioning affects of clenbuterol in broiler chickens, cattle, sheep and swine (Ricks et al., 1984a). Those data are now published in a series of papers (Dalrymple et al., 1984; Ricks et al., 1984b; Baker et al., 1984b) and additional data are available which demonstrate the tissue

Table 1. Effect of Porcine Somatotropin or hpGRF on Growth Performance and Composition in Swine

Animal type/ weight	*Dose (μg/kg/d)*	*Duration of Treatment (days)*	*Muscle Mass (kg)*	*% Carcass Lipid*[1]	*ADG (kg/d)*	*Feed/Gain*
Yorkshire barrows[2]	0	30	52.2[a]	28.4[a]	.91[a]	2.7[a]
32.2kg	22 pGH	30	52.8[b]	27.9[a]	1.00[b]	2.6[b]
Yorkshire-Duroc barrows[3]	0	30	24.5[a]	29.4[a]	.90[a]	3.01[a]
50 kg	30 hpGRF	30	28.5[ab]	25.6[ab]	.95[ab]	—
	30 pGH		33.2[b]	24.1[b]	1.00[b]	2.44[b]
Yorkshire-Duroc barrows[4]	0	35	26.0[a]	28.4[a]	.90[a]	2.86[a]
43 kg	10 pGH	35	27.7[a]	28.1[a]	.98[ab]	2.72[ab]
	30 pGH	35	28.4[ab]	25.8[a]	.95[ab]	2.58[ab]
	70 pGH	35	30.5[b]	22.5[b]	1.03[b]	2.36[b]

[1]Value is percentage lipid in soft tissues (muscle + adipose).
[2]Chung and Etherton, 1985
[3]Etherton et al., 1985
[4]Rehbun et al., 1985
[ab]Means within a column (in each experiment) with different superscripts differ ($p<.05$).

repartitioning effectiveness of another beta-adrenergic agonist, cimaterol.

The repartitioning of tissue growth by clenbuterol and cimaterol varies somewhat between species. Results summarized in Table 3 demonstrate that steers fed 10 ppm clenbuterol for 98 days exhibit 11% larger rib eye areas, 36% less fat depth over the twelfth rib and 23% less kidney and pelvic fat than controls (Ricks et al., 1984). Carcass composition, estimated from chemical analyses of the 9, 10, 11th rib section, is improved to contain 13% more protein, 20% less fat and 10% more water. Rate of gain and feed efficiency in steers is not altered with clenbuterol.

Response of lambs to clenbuterol was very similar in three trials reported by Baker et al., (1984b). Clenbuterol fed to wethers at 2 or 10 ppm for 56 days increased carcass yield by 3 or more percentage units (p .01), increased longissimus cross-sectional area by 33% to 41% and decreased kidney and pelvic fat weight by 15% to 33%. Carcass composition estimated from chemical analyses of the hindquarters was improved to contain 9.5% to 12% more protein, 19% to 27% less fat and 8% to 12% more water. Average daily gain was improved about 10% in all three trials and feed efficiency was improved by 10% to 14%.

Barrows and gilts fed clenbuterol at .1 or 1 ppm from 50 kg to market weight had carcasses which contained 11% to 21% larger loin eye areas and 5% to 11% less backfat thickness (Ricks et al., 1984b). Composition of the carcasses was improved to contain about 6% more protein, 6% to 11% less fat and 4% to 5% more water. Growth performance was unaffected by clenbuterol addition to swine diets.

We have conducted two studies at Cornell which were designed to compare the effects of short-term (5-6 weeks) and long-term (10-12 weeks) administration of cimaterol on tissue repartitioning in wether and ram lambs (Beermann et al., 1985a). Table 4 summarizes the response of lambs to 10 ppm cimaterol fed in a complete, mixed, high-energy diet (16% crude protein 3.4 Mcal/kg DE, as-fed basis). Carcass yield was consistently increased by 3 to 4 percentage units

Table 2. Effect of Somatotropin on Carcass Yield, Composition and Meat Quality in Cattle[1]

	Placebo	*Somatotropin*	
Initial weight (kg)	180	180	
Dressing percentage	49.2	49.2	NS
Composition			
Percent Muscle	67.1	68.6	**
Percent Fat	14.2	12.5	***
Percent Bone	18.7	18.5	NS
Percent carcass in loin and round	49.0	49.5	*
Percent muscle in loin and round	33.7	34.5	**
Composition of longissimus muscle			
Percent Nitrogen	3.59	3.60	NS
Percent Lipid	1.82	1.45	***
Percent Water	74.8	74.9	NS
Quality traits of longissimus muscle			
Shear Force (kg)	7.9	8.6	NS
Tenderness	1.1	1.1	NS
Juiciness	2.6	3.0	NS
Flavor	2.7	2.9	NS
Color	3.2	3.3	NS
Overall	1.6	.7	NS

[1]Sejrsen and Bauman, unpublished data.
*p<.05
**p<.01
***p<.001

Table 3. Effect of Clenbuterol on Repartitioning Tissue Growth in Cattle and Sheep

Animal type/ weight	*Level in Diet (ppm)*	*Treatment Period days*	*Carcass Protein[1] (%)*	*Carcass Fat[1] (%)*	*ADG (kg)*	*Feed/Gain*
Hereford Steers[2] 350 kg	0	98	15.4[a]	35.2[a]	1.10[a]	11.8[a]
	10	98	17.4[b]	28.0[b]	1.01[a]	12.0[a]
	500	98	17.2[b]	26.3[b]	.87[b]	11.9[a]
Crossbred wethers[3] 32 kg	0	56	17.5[a]	21.1[a]	.196[a]	8.13[a]
	1	56	19.2[b]	16.8[b]	.180[a]	7.91[a]
	10	56	19.6[b]	15.4[b]	.195[a]	7.51[a]
	100		19.2[b]	16.3[b]	.209[a]	6.73[b]

[1]Determined by chemical analysis of 9-11th rib section in steers and analysis of hindquarters in lambs.
[2]Ricks et al., 1984 [3]Baker et al., 1984
[a,b]Means within a column (for each experiment) with different superscripts differ (p<.01)

Table 4. Effect of Cimaterol on Growth Performance and Repartitioning Tissue Growth in Lambs.

Animal type/ weight	Level in Diet (ppm)	Treatment Period (days)	Dressing%[1]	Longissimus Area (cm^2)	12th rib fat thickness (cm)	% kidney and pelvic fat	Percent muscle hypertrophy					
							BT	SM	ST	TB	SS	IS
Dorset wethers 17 kg	0	49	53.8[a]	13.2[a]	.44[b]	2.0[a]						
	10	49	57.0[b]	16.6[b]	.15[a]	1.3[b]	32.8**	27.1**	31.5**			
	0	84	59.5[b]	16.5[b]	.65[c]	2.6[a]						
	10	84	64.0[c]	21.8[c]	.44[b]	1.4[b]	24.1**	22.3**	21.5**			
Suffolk × Dorset rams 28 kg	0	35	50.7[a]	14.0[a]	.28[c]	2.6[a]						
	10	35	54.6[b]	18.7[b]	.05[a]	2.0[b]	25.4**	32**	14*	24**	12*	20**
	0	70	54.1[b]	15.6[a]	.46[b]	2.6[a]						
	10	70	57.8[c]	21.0[b]	.15[a]	1.7[b]	30.4**	37**	27**	35**	20**	26**

[1]Determined from shorn, overnight-fasted live weight and hot carcass weight.
[2]Abbreviations for muscle names: BF = biceps femoris, SM = semimembranosus, ST = semitendinosus, TB = triceps brachii, SS = supraspinatus, IS = infraspinatus.
[a,b]Means within a column (for each experiment) with different superscripts differ ($p<.05$).
*$p<.01$ **$p<.001$

with cimaterol. Longissimus area was increased 26% to 34%, fat thickness at the 12th rib was reduced by 32% to 60%. Percentage of kidney and pelvic fat was reduced by 20% to 44% and individual muscles were increased by an average of 25%, 28% and 22% for the biceps femoris, semimembranosus and triceps brachii, respectively. Percentage of carcass in the leg was consistently greater ($p<.05$) in cimaterol-fed lambs in both studies, again indicating a differential response by anatomical location. Average daily gain in these two trials was not improved by cimaterol and feed efficiency was between 5% and 15% better in cimaterol-fed lambs.

Mechanisms Responsible for Partitioning Tissue Growth

Measures related to skeletal muscle growth include cellularity, nucleic acid concentration and content, radial hypertrophy and longitudinal growth of muscle fibers and relative numbers and proliferative activity of satellite cells. All provide some insight for determining the regulatory control points for repartitioning agents. Unfortunately, availability of these particular types of data is very limited and we must compare data from tumor-induced hypersomatotropic rats with data from cimaterol-fed lambs to look for similarities and differences.

Seventy-fold and 160-fold elevation of serum somatotropin in Wistar-Furth rats is achieved by induction of GH1 and GH3 pituitary cell tumors at an early age. McCusker and co-workers have observed a 40% to 50% increase in body weight and 130% to 160% larger soleus muscles in tumor-induced rats by 11 weeks of age (McCusker et al., 1984, 1985). This dramatic increase in muscle weight is not the result of increased fiber number, but rather fiber diameter, which is 11% to 27% greater. Protein content of the muscle is greater while protein concentration is less (Table 5). Concentration and total muscle content of DNA and RNA, and RNA-DNA ratio are greater ($p<.05$) with GH3 tumor-induced

Table 5. Effect of Tumor Induction on Soleus Muscle Composition in Young Female Wistar-Furth Rats[1]

Measurement	Treatment	
	Control	GH3
Wet Weight (mg)	139.00[a]	189.00[b]
Dry Matter (%)	27.00[a]	25.00[b]
Protein (mg/g)	112.00[a]	99.00[b]
Protein (mg)	15.70[a]	18.70[b]
RNA (mg/g)	1.39[a]	1.54[b]
RNA (mg)	.20[a]	.29[b]
DNA (mg/g)	.68[a]	.57[b]
DNA (mg)	.09[a]	.11[b]
Protein/DNA	176.00	172.00
Protein/RNA	81.00[a]	66.00[b]
RNA/DNA	2.20[a]	2.70[b]

[1]Mean body weights for control and GH3 rats were 183 and 297 g, respectively. At one week of age 1 to 2 million GH3 were injected into treated rats. Composition was determined at 11 weeks of age.
[a,b]Means within a row with different letters are different, $p<.05$.

hypertrophy. Incidence of myonuclei and satellite cells was significantly greater in GH3 tumor-induced rats and satellite cell nuclei expressed as a percent of total muscle nuclei was 2-fold higher in soleus muscles from these rats.

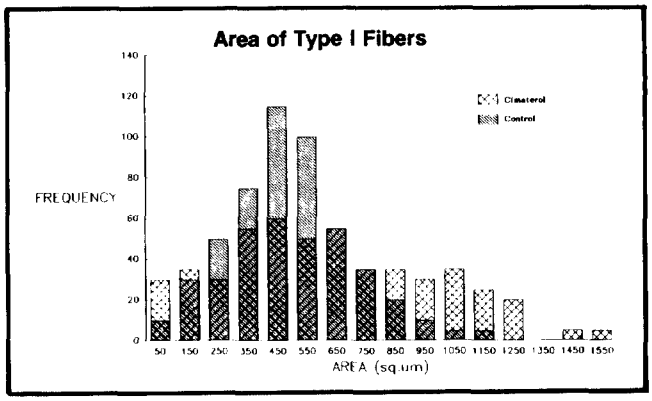
Tumor-induced somatotropin elevation increased total body protein, moisture and ash, while total lipid was unchanged. Therefore, the relative amount of moisture was higher, fat was lower and protein was similar in tumor-bearing rats. The parametrial fat pad of tumor-bearing rats was similar in weight and contained a similar number of fat cells when compared to control rats. However, fat cell size was smaller in tumor-bearing rats.

The muscle hypertrophy observed in cimaterol-fed lambs was also associated with increased muscle fiber size (Beermann et al., 1985c). Cross-sectional area of individual fibers was 29% to 30% greater in both type I and type II fibers in the semitendinosus muscle, which was 25% heavier after the 12-week treatment period (Figures 1, 2). Fibers in the longissimus muscle from these lambs had only 13% greater cross-sectional area; therefore, longitudinal growth of the fibers was also responsible for the 26% to 33% greater cross-sectional area of the longissimus. This is readily apparent when you consider the oblique alignment of the fibers with the long axis of the muscle.

A 35% and 25% greater muscle protein and RNA content was associated with the same relative increases in semitendinosus weight observed with 6 and 12-week cimaterol treatment, respectively (Table 6). Muscle DNA content, protein-DNA ratio and RNA-DNA ratio were only slightly higher in cimaterol-fed lambs.

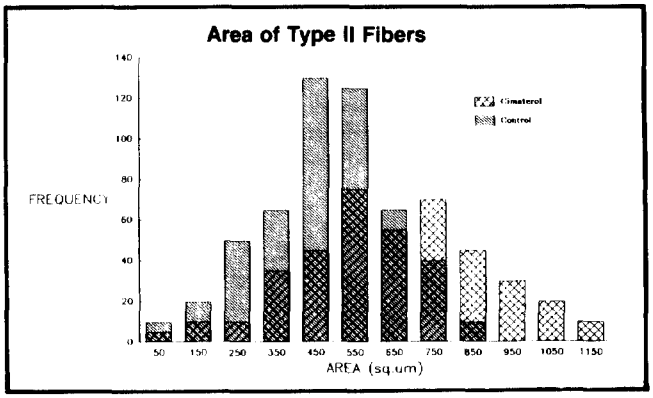
When compared to the tumor-bearing rat data, these data indicate that both repartitioning agents (GH and cimaterol) bring about increases in RNA to afford a greater capacity for protein synthesis. The RNA-DNA ratios were increased in both animal models, whereas muscle DNA content was significantly higher in only the hypersomatotropic rats. The

Figure 1



Frequency distribution of the cross-sectional area of Type I fibers in semitendinosus muscles of lambs fed 0 or 10 ppm cimaterol for 84 days.

Figure 2



Frequency distribution of the cross-sectional area of Type II fibers in semitendinosus muscles of lambs fed 0 or 10 ppm cimaterol for 84 days. Interval means represent areas of 100 fibers per lamb, n = 5 lambs.

Table 6. Effects of Cimaterol on Protein and Nucleic Acid Concentration and Content of the Semitendinosus Muscle in Dorset Wether Lambs

	Treatment Period				
	7 Weeks		*12 Weeks*		
Observation	*Control*	*Cimaterol*	*Control*	*Cimaterol*	$S_{\bar{X}}$
Number of Lambs	6	6	6	5	
Semitendinosus Wt. (g)	94.2[a]	127.8[b]	130.1[b]	163.1[c]	6.3
Protein Concentration (mg/g)	183	175	172	186	7
Protein Content (g)	17.24[a]	22.36[b]	22.37[b]	30.34[c]	1.15
DNA Concentration (μg/g)	409.3	319.8	315.3	316.4	34.8
DNA Content (mg)	38.6	40.9	41.0	51.6	4.9
RNA Concentration (μg/g)	568.9	572.1	492.6	539.7	23.3
RNA Content (mg)	53.6[a]	73.1[b]	64.1[a,b]	88.1[c]	4.3
Protein/DNA	446.6	546.7	545.6	588	
Protein/RNA	321.6	305.8	349	344.4	
RNA/DNA	1.39	1.79	1.56	1.71	

[a,b]Means within a row with different letters are different, ($p<.05$).

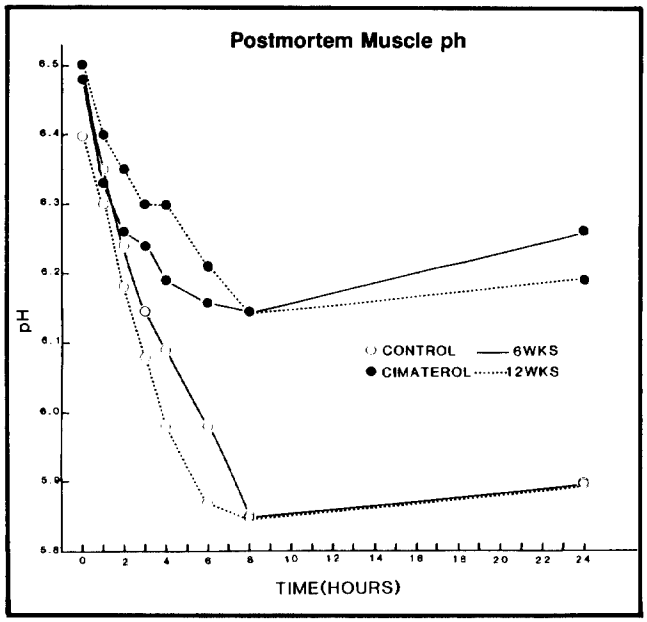
increased incidence of satellite cells and myonuclei in rat muscle thin sections appears to be somatotropin dose-dependent. The continuous extreme elevation of circulating somatotropin (in excess of 1000 ng/ml) which results from GH1 or GH3 tumor induction is adequate to stimulate muscle growth and nuclear proliferation in these Wistar-Furth rats. Daily exogenous somatotropin administration (.25 IU bGH/100 g body weight; 1.3 IU/mg) failed to stimulate body weight or muscle weight gain, muscle DNA accretion, or satellite cell proliferation despite transient 5 to 10-fold elevation of circulating somatotropin (Beermann et al., 1983; Beermann and Wilson, 1984). The requirement for a high dose of somatotropin to stimulate growth in rats has been confirmed by Baker and co-workers (1984). Chronic (6 week) administration of 250 to 500 g bGH/d failed to enhance growth while 1000 g/d increased weight gain by 22.8% ($p<.05$) in young females. Mature females showed no response to any of the three dose levels. Since GH does not act directly on myoblasts or satellite cells to stimulate proliferation (Allen et al., 1983), somatomedins have been postulated to provide the active mitotic stimulus for enhanced muscle growth. Not until recently, however, has a purified somatomedin (ovine) been shown to enhance satellite cell proliferation in vitro (Dodson et al., 1984). Availability of somatomedin has precluded studies being conducted to verify these findings in young growing animals in vivo.

Effects of somatotropin on skeletal muscle metabolism have been evaluated using in-vitro preparations (McCusker et al., 1984), but only limited data are available for beta-agonists. Tumor-induced hypersomatotropy in Wistar-Furth rats did not affect leucine metabolism, as measured by CO_2 production, production of alpha-ketoisocaproate or incorporation into protein in soleus muscle slices in vitro. Palmitate oxidation to CO_2 and incorporation into phospholipids was also unchanged. However, less palmitate was incorporated into triglycerides in tumor-bearing rate muscle. Tumor-induced somatotropy did reduce muscle glucose oxidation and conversion to CO_2, while glucose uptake was unchanged. Less glucose was incorporated into glycogen in treated rat muscle.

Glucose metabolism is also altered in muscle of beta-agonist-fed lambs. Muscle CO_2 production from glucose oxidation was increased by 58% and rate of glycogen synthesis from labeled glucose was 2 to 3-fold higher in longissimus muscle strips from clenbuterol-fed lambs (Hamby et al., 1985). Phosphorylase histochemistry indicated a 50% or greater increase in negatively stained fibers in muscles from cimaterol-fed lambs (Beermann et al., 1985c). A strong indication that muscle glycogen stores are reduced with cimaterol administration is also seen in post-mortem muscle pH profiles. Both 5 and 10-week administration of cimaterol resulted in slower-post mortem pH decline and significantly higher ultimate pH in the longissimus muscle (Figure 3) of lambs fasted overnight before slaughter.

Further indications of altered muscle metabolism are indicated by shifts in fiber type composition in muscles of cimaterol-fed lambs (Table 7). Marked reduction in percentage of type I fibers was observed in both portions of the semitendinosus muscle. The rapid decline in percentage of type I fibers (by over 70%) observed in the semimem-

Figure 3



Post mortem pH decline in longissimus muscle of lambs fed 0 or 10 ppm cimaterol for 84 days.

Table 7. Effect of Cimaterol on Muscle Fiber Type in Three Lamb Muscles[1]

	Muscle Identification			
	Semitendinosus			
Treatment Group	*Medial Portion*	*Lateral Portion*	*Semi-Membranosus*	*Longissimus*
	Percent Type I Fibers			
Baseline	15.0	3.8	13.9	9.8
6 Week Control	13.9	3.7	11.5	7.5
6 Week Cimaterol	6.4**	2.0**	8.9	8.0
12 Week Control	10.7	3.6	3.5	0.7
12 Week Cimaterol	3.7**	0.4**	0	.2

**$p<.01$ cimaterol vs. control

[1]Means represent counts of 2000 fibers per sample; N = 5 for each smallest subclass. Cimaterol was administered at 10 ppm in a complete, mixed, high-concentrate diet to Dorset wether lambs.

branosus and longissimus muscles during the course of the study may have precluded the cimaterol effects being exhibited in these muscles.

Carbohydrate metabolism in muscle may be influenced through increases in cyclic-AMP concentrations brought about with clenbuterol and cimaterol, but data supporting this have not been reported. Epinephrine stimulates glycogen phosphorylase activity and inhibits glycogen synthase via elevated cyclic-AMP. These specific effects may be subject to or overshadowed by the overall increase in metabolic rate in beta-agonist-treated animals. Significant acute elevation of heart rate and blood flow to the hindquarters has been observed in preliminary studies with cimaterol-fed lambs (Beermann, unpublished data).

Circulating Hormone and Metabolite Concentrations

Regulation of nutrient utilization by various tissues is unquestionably influenced by several metabolic hormones (Bauman, 1984 and Etherton and Walton, 1985). Somatotropin has been shown to be a key regulator of the coordination of nutrient repartitioning, both for increasing lactation (Bauman et al., 1985) and for altering the patterns of tissue growth. The selected synthetic beta-agonists clenbuterol and cimaterol also possess these capabilities, but probably act through different endocrine mechanisms. Again, data are not abundantly available, but significant differences between GH and beta-agonist influence on circulating metabolic hormone levels and substrate metabolism have been observed.

Daily injection of bovine somatotropin (29.2 IU/d; 1.3 IU/mg) for 14 days in growing Hereford heifers had no effect on circulating levels of plasma glucose or beta-hydroxybutyric acid, serum urea nitrogen, plasma prolactin, thyroxine (T_4) or triiodothyronine (T_3) (Eisemann et al., 1984a,b; 1985a,b). Plasma GH, insulin and nonesterified fatty acid (NEFA) concentrations were elevated, whereas leucine concentration was decreased with GH administration (Table 8). The authors state that these changes were chronic rather than acute alterations to daily GH injections. Irreversible loss of leucine was unchanged with somatotropin administration; however, oxidation of leucine to CO_2 was decreased. Nitrogen retention in these heifers was also increased and as a result whole-body protein synthesis was increased. There was an increase in irreversible loss and in oxidation of NEFA during treatment with bGH. Although total CO_2 production was not changed, the percentage CO_2 derived from NEFA was also increased. Total energy balance was not changed with bGH treatment and energy retained as nitrogen increased. Therefore, it may be implied that energy stored as fat decreased. Total heat production was unaffected by bGH and gross efficiency of metabolizable energy use was the same in control and treated heifers.

These data indicate that stored fatty acids were mobilized to provide greater utilization of NEFA for energy needs related to cellular activities. Because intake of metabolizable energy was at near maintenance level in this study, additional work must be conducted to determine if similar metabolic shifts occur with the greater energy intake required for normal or maximum growth rate. Other data from studies on lactating dairy cows would indicate that mobilization of stored lipid to increase NEFA utilization only occurs when the animal is in negative energy balance (Bauman and McCutcheon, 1985).

Table 8. Effect of Bovine Somatotropin on Plasma Concentration of Hormones and Metabolites in Hereford Heifers[1,2]

Hormones (ng/ml)	Placebo	bGH	SE
Insulin	3.8	6.1*	.9
Prolactin	8.5	19.5	2.6
Thyroxine	52.1	48.5	7.0
Triiodothyronine	0.92	0.87	0.18
Metabolites (mM)			
Glucose	3.1	3.6	.3
β-hydroxybutyric acid	0.70	0.74	.04
Serum urea nitrogen	2.7	2.3	0.2
Leucine (μM)	133.2	93.6**	8.7
NEFA (μeq/L)	79.4	115.5*	9.1

[1]Means represent an 8-hour blood sampling period for all variables except urea, leucine and NEFA.
[2]Eisemann et al., 1984.
*($p<.05$) **($p<.01$)

Chronic administration of porcine GH produced somewhat similar changes in young growing pigs (Chung et al., 1985). Plasma glucose and insulin concentrations were increased, plasma NEFA concentrations were slightly higher and blood urea nitrogen was significantly less in pigs receiving pGH. These results, however, are derived from single blood samples collected at 10-day intervals and plasma insulin concentation declined in control pigs while that in treated pigs remained unchanged over the 30-day treatment period. Therefore, based upon available data, comments regarding effects of somatotropin on carbohydrate and lipid metabolism in swine must be considered speculative at this time.

The tissue repartitioning effects of somatotropin, therefore, can best be characterized as a homeohretic response, a coordinated shift in metabolism and nutrient repartitioning which facilitates more rapid muscle growth and reduced fat accretion. Data available indicate an effect on post-absorptive metabolism of nitrogen to reduce amino acid oxidation and urinary nitrogen excretion, affording increased nitrogen retention. Shifts in lipid metabolism induced by exogenous somatotropin administration depend in part on the energy status of the animal. Mobilization of stored triglycerides and increased reliance on NEFA to provide energy for cellular activities occur when somatotropin is administered to animals in negative or near-maintenance energy balance. This response has not been demonstrated in young farm animals receiving adequate energy intake to support rapid growth. Somatotropin does not alter the gross efficiency of metabolizable energy use at near-maintenance intake of metabolizable energy. Somatotropin administration does not appear to cause major shifts in plasma concentrations of other important metabolic hormones; however, effects on tissue sensitivity to these hormones in farm animals (i.e.

receptor densities and binding affinities) have not been reported. Physiological concentrations of insulin are needed to maintain lipogenesis in sheep (Vernon, 1982) and swine (Etherton and Walton, 1985) adipose tissue cultures. These authors have also shown that physiological concentrations of somatotropin antagonize the ability of insulin to maintain lipogenesis or lipogenic capacity in ovine or bovine adipose tissue cultures. Hydrocortisone enhancement of these effects has also been demonstrated (Etherton and Walton, 1985). Further work must be conducted to define the interactions between somatotropin and other hormones involved in the regulation of lipid metabolism.

Plasma metabolic hormone and metabolite concentrations in lambs fed 10 ppm cimaterol for 6 or 12 weeks are shown in Table 9 (Beermann et al., 1985a). These data represent samples taken over a 6-hour period. Insulin and cortisol was assayed in all samples, prolactin in alternate samples and glucose in hourly samples. NEFA concentrations were determined at the beginning, middle and end of the sampling period; T_4 and T_3 at the beginning and end.

Insulin levels were 55% lower ($p<.01$), T_4 levels were 25% higher (p .01) and NEFA levels were 60% higher ($p<.01$) and increased during the sampling period in cimaterol-fed lambs. Plasma glucose, T_3, prolactin and cortisol were unchanged with cimaterol treatment. These data indicate a maintenance of glucose homeostasis and a mobilization of lipid stores which would be expected to be associated with greater use of NEFA as an energy source. When determined together, plasma NEFA concentrations and NEFA turnover (irreversible loss) have exhibited a high positive correlation (Eisemann et al., 1984a; Bauman, personal communication).

Insulin is needed to maintain lipogenesis in adipose tissue of lambs (Vernon, 1979, 1980) and ovine somatotropin antagonizes the lipogenic effect of insulin in ovine adipose tissue culture (Vernon, 1982). Catecholamines have been shown to inhibit beta-cell release of insulin ($alpha_2$-receptor response), and physiological levels of catecholamines (which stimulate lipolysis) inhibit insulin binding by 40% to 70% in rat adipocytes (Pessin et al., 1983). Insulin also inhibits lipolysis, while beta-adrenergic agents stimulate lipolysis in both ruminant and nonruminant species (Blum et al., 1982; Mersmann, 1984). Thyroid hormones enhance the effectiveness of lipolytic hormones (Fain and Garcia-Sainz, 1983) and increase metabolic rate.

Taken together, the changes in insulin, T_4 and NEFA concentrations would suggest that cimaterol (and other repartitioning beta-agonists) may act to decrease lipogenic activity in adipose tissue, increase lipolysis and use of NEFA as an energy substrate, thereby sparing glucose and amino acids otherwise destined for use in gluconeogenesis in ruminants. This would provide the needed energy and substrate for protein synthesis required by the increased metabolic rate and greater net protein accretion in beta-agonist-fed lambs. Chronic increases in heart rate and blood flow have been observed in cimaterol-fed lambs (Beermann, unpublished data) and acutely elevated body temperature has been observed in clenbuterol-infused lambs (Reeds, personal communication). Although protein synthesis (fractional rate) has been shown to be increased with clenbuterol in rats (Emery et al., 1984), whether this is a direct effect on the synthetic machinery or an indirect effect via increased substrate availability remains to be shown. Isoproterenol has been shown to increase amino acid uptake and cause hypertrophy in skeletal and cardiac muscle (Deshaies et al., 1983).

The greater net accretion of muscle mass may also be influenced by decreased rates of protein degradation. Epinephrine and isoproterenol (beta-agonists) have been shown to reduce protein catabolism (Hill and Malamud, 1974; Li and Jefferson, 1977; Tischler, 1981). Data are not yet available for the effects of clenbuterol on protein degradation in meat animal species.

In summary, we have more fully characterized the tissue repartitioning effects of somatotropin and the select beta-agonists clenbuterol and cimaterol in meat animals with new, recently-obtained data. Somatotropin and the beta-agonists

Table 9. Effects of Cimaterol on Plasma Concentration of Hormones and Metabolites in Wether Lambs[1,2]

	Treatment Period				
	6 Weeks		*12 Weeks*		
Hormones	*Control*	*Treated*	*Control*	*Treated*	$S_{\bar{X}}$
Insulin (ng/ml)	3.8	1.7*	3.6	1.5*	.5
Prolactin (ng/ml)	158.3	181.1	290.9	209.6	71.7
Thyroxine (μ/100 ml)	5.68	7.12*	7.04	9.07*	.41
Triiodothyronine (ng/ml)	1.23	1.37	1.17	1.31	.11
Cortisol (ng/ml)	15.1	13.6	13.2	15.5	1.6
Metabolites					
Glucose (mg %)	85.4	82.3	73.4	76.2	6.6
FFA (μeq/L)	328	527*	246	409*	56.1

[1]Means are for samples collected over a 6-hour period; feed was withdrawn at the start of sampling.
[2]Beermann, et al., 1985.
*Treatment means different from control ($p<.05$).

both appear to exhibit the dual reciprocal effect on protein (nitrogen) and fatty-acid metabolism to act as a homeohretic regulator to repartition nutrient use between skeletal muscle and adipose tissue. Metabolism in these and other tissues (and organs) are affected in such a way as to support increased muscle growth and decreased fat accretion. Cellularity per se appears to be unaffected by these repartitioning agents. However, the observed effects of elevated plasma somatotropin and IGF-1 on satellite cells indicates one possible mode of action leading to greater muscle accretion.

Whether the repartitioning beta-agonists alter satellite cell numbers or proliferation rate in association with greater muscle growth remains to be shown. Indeed, whether either somatotropin or the beta-agonists may be effectively used to alter tissue cellularity or to alter metabolism in the fetus to improve post-natal tissue growth patterns or to improve survival must be addressed.

Much additional effort must be directed to more fully characterize the metabolic mode of action of both somatotropin and the repartitioning beta-agonists. The complexity of the biological processes involved indicates that the puzzle may not be solved quickly.

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Discussion

M. Dikeman: It appeared in the slides that there were distinct differences in carcass length and I wondered if you had any measures of bone development, such as length of long bones or ossification differences?

D. Beermann: That is an interesting observation. We noticed that the carcasses were shorter in the first study but we made no measurements. In the second, we collected both carcass and metatarsal bone length (lower rear leg). There were no differences in metatarsal bone length but carcass length was shorter in the cimaterol-treated lambs; I interpret that to be the result of the slightly different conformation of the carcass due to the increased muscle. When these carcasses were fabricated into wholesale cuts, we had difficulty making typical blade chop cuts from the front end of the cimaterol carcasses. We did look at ossification and there were no marked differences.

S. Smith: I have a couple of questions, Don. First, where you show a depression in plasma insulin and an increase in FFA. Since insulin is required in nonruminants (rats especially) to depress lipolysis by making more blood glucose available to the tissue, are you certain that the elevated FFA that you see is not due to the fact that you depress insulin levels?

Beermann: We really can't be certain, Steve, but this is a point that needs to be made. Certainly there are species differences; very marked differences, especially for GH effects in rats versus ruminants. We really can't explain why a beta agonist causes these effects.

Smith: We call these repartitioning agents and perhaps that implies what we are seeing in the hypertrophy of muscle and atrophy of adipose tissue is a shunting of energy from one depot to another. Is this a cause or effect? Perhaps cimaterol and clenbuterol are having direct tissue effects and the result is causing more energy to be directed into protein synthesis simply because of increased demand; and, more in my area of interest, decreased adipose tissue accretion because of a direct effect rather than an indirect one.

Beermann: That is certainly a logical explanation for the decreased fat accretion. We would expect a direct lipolytic effect of beta agonists on adipocytes to mobilize FFA. The ruminant is going to depend on FFA as the primary source for energy; so, with the increased metabolic rate, all these are working in the same direction to support the increased rate of metabolism which is associated with protein synthesis and might spare amino acids from being used by the liver for gluconeogenesis, which, of course, is an ongoing process. All this seems to fit in concert, we don't really see any conflicts here.

Smith: Really, the only contradiction we see in our clenbuterol studies is that fat cell size increased while we had expected to see a decrease due to lipolysis. However, we have found no data in the literature indicating changes in fat cell size following lipolysis.

Unknown: What has been the experience in other species with repartitioning agents?

R. Dalrymple: These compounds work in all meat animal species with lambs appearing to be most responsive in terms of repartitioning effect. In finishing swine (50 to 100 kg) we have been seeing increases in longissimus area of 5% to 15% and decreases in backfat of about 10%. One difference from the lamb data is that we see no differences in carcass length. This may be related to the less dramatic effect cimaterol is having in swine as far as increasing musculature is concerned. Cimaterol is also improving feed efficiency in finishing swine by about 5% while having no effect on gain.

Unknown: What about stress susceptibility and meat quality in swine?