Effects of Beta Adrenergic Agonists on Endocrine Influence and Cellular Aspects of Muscle Growth

D.H. Beerman*

The normal allometric growth patterns of skeletal muscle and adipose tissue have been intensively studied since Hammond first reported his classical description of tissue growth relative to whole body weight gain. In the past three or four years, alteration of the normal allometric growth patterns of skeletal muscle and adipose tissue has been demonstrated in meat animals with administration of select catecholamine-like compounds and somatotropin. The repartitioning of nutrient use toward greater muscle growth and concurrent reduction in lipid accumulation can be achieved by the administration of a single compound (beta-adrenergic agonists or somatotropin), but it is now evident that circulating concentrations of other key metabolic hormones and sensitivity to these hormones is altered as well. Many hormones and some growth factors are well known to influence skeletal muscle growth. The question of direct or indirect (secondary) mode of action of these β-agonists to stimulate muscle growth is currently unresolved and is being studied intensely. The β-adrenergic agonists clenbuterol, fenoterol and cimaterol were among the first shown to exhibit marked effects on muscle and adipose tissue growth in animals. Attempts to demonstrate direct influence of these compounds on muscle growth processes have not yielded significant positive results. Protein turnover measured in whole muscle explants was not altered with varied doses of clenbuterol (P.J. Reeds, personal communication). Protein turnover in cultured myogenic cells was not significantly altered by direct addition of cimaterol to rat and mouse myoblasts (Forsberg and Merrill, 1986; Roeder et al., 1987) or primary chick muscle cells (Young et al., 1987). Serum from rats fed clenbuterol was also ineffective in altering protein turnover in L8 cells (McElligott and Chaung, 1987). Effects on percentage of nuclei within multinucleated myotubes and total number of nuclei within myotubes were also not significantly affected in the latter two studies.

Adrenergic hormones or agonists may influence secretion of many hormones in either a positive or negative way, depending on dose, species and analogue (Huang et al., 1983). I will review results from recent studies in our laboratory and others with regard to changes in either circulating concentrations of key metabolic hormones or measures of response to altering circulating hormone concentrations in animals fed cimaterol or clenbuterol. I will also attempt to relate these findings to the associated muscle growth response.

Insulin

Table 1 displays the chronic effects of feeding 10ppm cimaterol to Dorset wether lambs for 6 or 12 weeks on several metabolic hormones known to influence growth (Beermann et al., 1987). Lambs were fed a mixed high-concentrate diet ad libitum, but feed was withdrawn approximately one hour prior to collection of blood samples. Samples were collected at twenty-minute intervals for 6 hours and plasma stored at –10°C until assayed by specific radio-immunoassay. Insulin concentration was reduced by 55% at both 6 and 12 weeks in lambs fed cimaterol. This observation has been confirmed in subsequent studies in which lambs were prepared for arterio-venous sample collections from the hindquarters (Table 2). Insulin concentration was reduced by 41% and 48% after two and four weeks, respectively, of feeding 10ppm cimaterol in the same mixed diet offered every two hours at approximately 90% of ad libitum.

In contrast, insulin concentration did not decline during the 4 weeks of study in lambs which did not receive cimaterol (Table 3). The lower insulin concentration did not result in elevated glucose concentration in either experiment. Fenoterol, a β-adrenergic agonist, reduces plasma insulin concentration by 30% in rats (Emery et al., 1984).

The acute response to cimaterol administration is dramatically different from the chronic response, and typifies the action of a β-agonist. A marked acute elevation in plasma insulin concentration resulted from abomasal infusion of cimaterol (1.5 mg/day) in lambs wholly nourished by intragastric infusion of nutrients (Beermann et al., 1986). Insulin concentration was increased by over 400% during the first 10 hours of cimaterol infusion and remained 50% higher from 18 to 20 hours of infusion. (Figure 1). A marked hyperglycemic response accompanied the dramatic increase in insulin. Plasma glucose was elevated within 2 hours of initiating cimaterol infusion and rose to an average of 37% above control levels within 6 hours (72 vs. 98 mg/dl) before returning to normal levels (Figure 2). The marked acute elevation of plasma glucose likely occurred as the result of cimaterol stimulating hepatic and skeletal muscle glycogenolysis. It is interesting to note that epinephrine, a mixed adrenergic agonist, and insulin have opposite effects on gluconeogenesis and glycogenolysis in both liver and skeletal muscle, and on lipolysis in adipose tissue.

The marked elevation of insulin may have been driven by

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Table 1. Effects of Cimaterol on Plasma Concentration of Metabolic Hormones, Glucose and Non-Esterified Fatty Acids in Dorset Wether Lambs.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Insulin (ng/ml)</th>
<th>T4 (µg/dl)</th>
<th>T3 (ng/ml)</th>
<th>Somatotropin (ng/ml)</th>
<th>Prolactin (ng/ml)</th>
<th>Cortisol (ng/ml)</th>
<th>Glucose (mg/dl)</th>
<th>NEFA (µEq/l)</th>
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<tr>
<td>Control</td>
<td>6</td>
<td>1.01</td>
<td>5.01</td>
<td>1.12</td>
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<td>3.80</td>
<td>5.68</td>
<td>1.23</td>
<td>2.36</td>
<td>158.3</td>
<td>15.1</td>
<td>85.4</td>
<td>328</td>
</tr>
<tr>
<td><strong>6 Weeks</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Control</td>
<td>6</td>
<td>1.72*</td>
<td>7.12*</td>
<td>1.37</td>
<td>5.51*</td>
<td>181.0</td>
<td>13.6</td>
<td>82.3</td>
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<td>7.04</td>
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<td>290.9</td>
<td>13.2</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>5</td>
<td>1.55*</td>
<td>9.07*</td>
<td>1.31</td>
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<td>209.6</td>
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*Means within rows not having a common superscript differ (p<.01).

Table 2. Plasma Metabolic Hormone Concentrations in Wether Lambs Fed Cimaterol.

<table>
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<tr>
<th></th>
<th>N</th>
<th>Insulin (µu/ml)</th>
<th>T4 (ng/ml)</th>
<th>T3 (ng/ml)</th>
<th>Somatomedin-C (units/ml)</th>
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</thead>
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<td>24.5b</td>
<td>64.1</td>
<td>1.04</td>
<td>4.38</td>
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<td>4 Weeks</td>
<td>6</td>
<td>21.5b</td>
<td>69.9</td>
<td>1.05</td>
<td>5.63</td>
</tr>
<tr>
<td>$\bar{X}$</td>
<td></td>
<td>3.9</td>
<td>4.3</td>
<td>.11</td>
<td>.33</td>
</tr>
</tbody>
</table>

*Means represent 4 animals
Means with different superscripts differ (p<.05)

Table 3. Plasma Metabolic Hormone Concentrations in Companion Control Lambs.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Insulin (µu/ml)</th>
<th>T4 (ng/ml)</th>
<th>T3 (ng/ml)</th>
<th>Somatomedin-C (units/ml)</th>
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<td>53.2</td>
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<td>21.3</td>
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<tr>
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<td>66.9</td>
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<tr>
<td>$\bar{X}$</td>
<td></td>
<td>14</td>
<td>6.9</td>
<td>.14</td>
<td>.14</td>
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</tbody>
</table>

*Means represent 4 animals
Means with different superscripts differ (p<.05)

Cimaterol and clenbuterol may act directly on the pancreas to inhibit insulin secretion in the chronic situation. Epinephrine has been shown to increase glucagon secretion in A cells and to inhibit insulin secretion in B cells at physiological concentrations (Schuit and Pipeleers, 1986). Before cytofluorimetric cell sorting procedures were developed, in vitro work with pancreatic cells involved mixed cell populations. In sorted cells, the inhibition of insulin secretion was clearly shown to be $\alpha_2$-receptor mediated, requiring the presence of an adenylcyclase activator such as glucagon.

Figure 1

Plasma insulin concentration in 35 kg crossbred ewe lambs before and during the first 22 hours of cimaterol administration. Lambs were sustained by intragastric infusion of nutrients and received 1.5 mg cimaterol per day via the abomasal infusion of casein.

Figure 2

Plasma glucose concentration in 35 kg crossbred ewe lambs before and during the first 14 hours of cimaterol administration. Measurements were made on the same samples used for insulin concentration determination represented in Figure 1.
Although cimaterol and clenbuterol are classified as β-agonists, pharmacological characterization of receptor specificity has not been published. It is quite possible that cimaterol stimulates both α and β receptors.

Two lines of evidence strongly indicate that cimaterol also alters glucose response to insulin in growing lambs. This is important for two reasons. First, there is an excellent correlation between glucose entry rate and growth rate in lambs and steers (Kempton et al., 1978). Second, in prefattening weaned lambs, glucose metabolism per unit metabolic weight (kg⁻¹) tends to increase before declining to adult levels. These changes are in parallel with postweaning changes in voluntary feed intake and growth rate (White and Leng, 1980).

The altered glucose response to insulin is supported by the results of net glucose uptake and insulin challenge experiments. First, net uptake of glucose by the hindquarters is maintained or slightly increased in the face of markedly reduced circulating insulin concentration. Comparisons made between pre-treatment and 2 and 4-week treatment intervals show that blood flow to the hindquarters is significantly elevated and glucose arterio-venous (a-v) concentration difference is not markedly altered, resulting in net glucose uptake remaining equal to or greater than pre-treatment levels when lambs are fed cimaterol (Table 4). Second, the glucose response to exogenous administration of insulin is different before and after chronic cimaterol administration. On the day following blood sample collection for a-v difference determinations, a single dose of insulin (200 mUnits/kg body weight) was administered via the arterial catheter in a volume of approximately 1.5 ml. Plasma glucose and insulin concentrations were determined at 45, 30, 15, 0, 4, 8, 12, 15, 20, 30, 60, and 90 minutes relative to the insulin challenge. Areas under the curve for plotted glucose and insulin concentrations were determined by planimetry and expressed as a glucose-insulin ratio. An increase in this ratio signifies a greater reduction in plasma glucose to the standard insulin dose and, therefore, denotes an increased response. Table 5 presents the ratios determined at 0, 2 and 4 weeks of treatment and after 7 days withdrawal of cimaterol in treated and control lambs. The response to insulin was significantly greater at 2 weeks, but not 4 weeks of cimaterol administration. However, the trend toward an enhanced response was still evident at 4 weeks and the response returned to near that observed pre-treatment after 7 days of withdrawal of cimaterol. The glucose response was not significantly different between sampling intervals in control lambs and, importantly, ratios were similar to those observed in the pre-treatment period in treated lambs.

Although the procedures used in these experiments do not provide direct measurement of the response in muscle, inference can be made that the results reflect changes in skeletal muscle. High physiological concentrations of epinephrine and acute exercise increase insulin binding to skeletal muscle plasma membranes, and this response has been shown to be mediated through β-adrenergic receptors (Webster et al., 1986). Adipose tissue in the ruminant is only a minor source of glucose utilization, accounting for ~1% of the total (Beneke and Lindsay, 1967) and estimates of the proportion of whole-body irreversible loss of glucose accounted for by muscle vary between 20% and 40% (Oddy et al., 1985; Pethic, 1984). Eisemann et al. (1986) observed both acute and chronic increases in oxygen uptake by the hindquarters of steers fed approximately 0.033mg clenbuterol/kg body weight per day, in four equal portions. This response was associated with elevated heart rate and blood flow, as observed in lambs fed cimaterol, and later studies in cattle (Eisemann et al., 1987) showed that hind limb blood flow was preferentially increased relative to blood flow to the portal drained viscera, allowing greater nutrient availability to skeletal muscle.

The acute and chronic changes in plasma insulin concentrations and glucose response resulting from cimaterol administration were observed in lambs which exhibited marked increases in skeletal muscle growth and in lambs in which nitrogen (N) retention was markedly increased (Figures 3 and 4). Weight of individual muscles was increased by 21% to 33% in the wether lambs for which endocrine data are presented in Table 1; while lipid depots were reduced by 30% to 60% (Beermann et al., 1986). Lambs used in the hindquarters experiments were from the same flock and received the same level of cimaterol as the lambs referred to in Table 1. Cimaterol significantly increased N retention by 27% in the lambs wholly sustained by intragastric infusion of nutrients (Figure 4). We have recently completed an experiment in which muscle weights were increased by 18% to


<table>
<thead>
<tr>
<th></th>
<th>Blood Flow (ml/min)</th>
<th>Plasma Flow (ml/min)</th>
<th>Glucose A-V DIFF (mg %)</th>
<th>Glucose Uptake (mg/min)</th>
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</thead>
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<tr>
<td>Baseline</td>
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<td>456a</td>
<td>5.4</td>
<td>25.39</td>
</tr>
<tr>
<td>2 Weeks</td>
<td>797b</td>
<td>592b</td>
<td>5.2</td>
<td>30.64</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>694ab</td>
<td>512ab</td>
<td>4.7</td>
<td>30.50</td>
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a,bMeans with different superscripts differ (p<.05)

### Table 5. Effect of Cimaterol on Glucose Response to Exogenous Insulin in Young Wether Lambs.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>N</th>
<th>Glucose/Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3</td>
<td>1.29a</td>
<td></td>
</tr>
<tr>
<td>2 Weeks</td>
<td>3</td>
<td>1.90a</td>
<td></td>
</tr>
<tr>
<td>4 Weeks</td>
<td>3</td>
<td>1.80a</td>
<td></td>
</tr>
<tr>
<td>7-d Withdrawal</td>
<td>3</td>
<td>1.97a</td>
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a,bMeans with different superscripts differ (p<.05)
Plasma non-esterified fatty acid (NEFA) concentration in 35 kg crossbred ewe lambs before and during the first 22 hours of cimaterol administration. Measurements were made on the same samples used for glucose and insulin concentration determinations represented in Figures 1 and 2.

35% in lambs fed 10 ppm cimaterol for 21 days (O'Connor and Beermann, unpublished data).

Thyroid Hormones

Thyroxine concentration was chronically elevated by 25% (p<.01) in lambs fed cimaterol; however, triiodothyronine (T₃) concentration was elevated by only 10% to 12% (p>.05). These elevations may be related to increased metabolic rate and increased heat production, which have been observed in lambs fed clenbuterol (MacRae et al., 1986). This must be questioned pending further investigation, because elevated T₄ or T₃ levels have not been observed in lambs used in our hindquarters studies (Table 2). Beta-agonists stimulate lipolysis in ruminants (Blum et al., 1982) and thyroid hormones enhance the effectiveness of lipolytic hormones (Fain and Garcia-Sainz, 1983). Skeletal muscle can use significant amounts of non-esterified fatty acids (NEFA) as an energy substrate in sheep (Bird et al., 1981) and both acute and chronic elevation of NEFA concentrations have been observed in lambs fed cimaterol (Beermann et al., 1986; Figure 3).

Somatotropin and Prolactin

Mean plasma somatotropin concentration was 2.33 times higher (p<.01) in lambs fed cimaterol for 6 weeks than in controls. Plasma somatotropin levels were not significantly elevated after an additional 6 weeks of feeding (Table 1). Area under the curve for these 6-hour mean concentrations was also 2.3 times higher in treated lambs at 6 weeks (p<.01) with no difference at 12 weeks. Alpha adrenergic influence on hypothalamic regulation of somatotropin secretion has been well documented (Martin, 1980) and includes demonstrated action of several central nervous system neurotransmitters. Recently, it has been shown that the β-agonists isoproterenol and epinephrine cause a prompt but brief increase in somatotropin secretion from perfused dispersed rat anterior pituitary cells (Perkins et al., 1983).

Figure 3

Figure 4

Net nitrogen retention in 35 kg crossbred ewe lambs for 7-day intervals before, during and after cimaterol administration. Lambs were sustained by intragastric infusion of nutrients and received 1.5 mg cimaterol per day via the abomasal casein infusion.

However, Smith and coworkers (1987) failed to see an increase in basal secretion, or GRF-induced secretion of somatotropin in an anterior pituitary perfusion system when comparisons were made between untreated and clenbuterol fed heifers.

Daily subcutaneous injections of bovine somatotropin which significantly improved growth rate, feed conversion and body composition in female lambs, elevated mean 28-hour somatotropin concentrations about 5-fold after 3 and 9 weeks of treatment (Johnsson et al., 1985). It is not possible to determine whether the 2.3 times elevation in somatotropin achieved with cimaterol had a significant effect on growth performance or composition, but it is interesting to note that the elevation observed was relatively constant compared to the transient elevation obtained with daily injection of somatotropin.

Figure 5

Plasma somatomedin-C (IGF-I) concentration in Dorset wether lambs fed 10 ppm cimaterol in a mixed, high-concentrate diet for 0, 6 or 12 weeks. Data represent independent observations from different lambs sampled at the three treatment intervals. Measurements were made in samples for which endocrine and metabolite data are presented in Table 1.
Other interesting comparisons can be made between the effects of cimaterol and somatotropin on circulating insulin and prolactin concentrations. Whereas cimaterol markedly reduces plasma insulin concentration, somatotropin administration increases insulin levels. Johnsson et al. (1985) observed a 79% and 58% increase in plasma insulin after 3 and 9 weeks of somatotropin treatment, respectively. Plasma prolactin concentration was also significantly elevated (164% and 16%) at these treatment intervals. The authors found that treating the lambs with bromocriptine not only reduced plasma prolactin concentrations as expected, but plasma insulin concentrations were reduced as well.

The combination of somatotropin and bromocriptine produced plasma insulin concentrations which were significantly higher than controls, but lower than those observed with somatotropin alone. Whereas bromocriptine alone had no effect on growth performance, the combination with somatotropin tended to reduce the somatotropin effects on food conversion and growth rate.

Plasma prolactin concentration was not significantly affected by cimaterol (Table 1); however, the effects of photoperiod and/or body weight were quite evident. The baseline group of lambs, representing plasma levels in March, exhibited much lower levels than lambs sampled 6 and 12 weeks later. Elsemann et al. (1984) failed to see any significant influence of bromocriptine or exogenous prolactin on growth in wether lambs. Although a role of prolactin in mediating the growth-stimulating effects of other anabolic compounds such as thyrotropin releasing hormone and diethylstilbestrol has been suggested (Bauman et al., 1982), a role in influencing growth in general seems as yet unresolved.

**Somatomedin-C**

Circulating concentrations of somatomedin-C (IGF-1) increased significantly with increasing weight (and age) in control and cimaterol-treated lambs, but levels were 46.5% and 21.5% lower in lambs fed cimaterol (p<.01) as shown in Figure 5. The positive relationship between body weight and IGF-1 levels is in agreement with other data for sheep (Olsen et al., 1981). The effects of cimaterol or other beta agonists on IGF-1 levels has not been previously reported. The reduction in IGF-1 levels parallels the reduction in plasma insulin concentration, and this is in contrast to the expected positive correlation with the elevated somatotropin observed in these lambs at 6 weeks.

Hypophysectomy reduces plasma IGF-1 concentration in ewes (Underwood et al., 1982) and exogenous somatotropin administration increases plasma IGF-1 concentration in lambs (Wein et al., 1983). The close association between declining IGF-1 concentrations with increasing time after feed removal and the concurrent 25% to 30% reduction in insulin concentration add credence to the suggestion that a close causal relationship between somatotropin and IGF-1 may not be true for all situations. Plasma somatotropin concentration did not decline during the 6-hour period of blood sample collection. Data from our studies and others support the existence of a strong relationship between plasma insulin and IGF-1 concentrations. In lambs and swine injected daily with exogenous somatotropin, plasma insulin concentration is also significantly elevated (Johnsson et al., 1985; Cahen-Wray et al., 1987). Infusion of insulin in fetal pigs elevates circulating somatomedin biological activity (Spencer et al., 1983), while pancreatectomy reduces IGF-1 but not IGF-II levels in fetal sheep (Gluckman et al., 1985).

An increase in skeletal muscle DNA and protein content would be expected in situations where somatotropin-induced skeletal muscle growth is observed. However, two groups have observed no increase in muscle DNA content concurrent with 25% to 30% increases in muscle weight and protein content in lambs fed cimaterol for 6 or 8 weeks (Beermann et al., 1987; Kim et al., 1987). The expected net increase in total muscle DNA was present after an additional 6 weeks of treatment in the study conducted by Beermann. These results strongly suggest that cimaterol increases muscle growth without initiating a mitotic response which leads to greater protein synthesis. Rather, these and other data indicate that the beta-agonists may act to reduce muscle protein degradation. The appropriate muscle DNA complement may accrue after the gain in muscle protein.

The inter-relationships between level of nutrient intake, plasma concentrations of insulin, somatotropin and IGF-1 have been reviewed recently (Phillips et al., 1986). The current information available does not contradict the relationships observed in our studies and evidence is presented which suggests that further work is needed to define the mechanism(s) by which the partitioning of adrenergic agonists alter plasma insulin, somatotropin and IGF-1 concentrations.

**Glucocorticoids**

Plasma cortisol concentrations were unaltered by cimaterol treatment (Table 1), but the possible involvement of glucocorticoids in mediating beta-adrenergic stimulation of muscle growth cannot be ruled out. Glucocorticoids have been shown to stimulate protein turnover in adrenalectomized and diabetic rats (Odedra and Millward, 1982). Clenbuterol has been shown to have no effect on growth rate, muscle weight or fat content of adrenalectomized rats (Sharpe et al., 1986). However, on giving dexamethasone therapy to restore glucocorticoid concentration to near physiological levels in rats, the growth-promoting effects of clenbuterol were again apparent. They observed no significant change in plasma corticosterone concentrations in normal rats fed the beta-agonist. It appears that the glucocorticoids may have a permissive effect on the partitioning effects of the beta-adrenergic agonists.

**Summary**

The data reviewed in this paper clearly show that cimaterol administration causes a marked reduction of circulating insulin concentration. This change does not impair the net uptake of glucose by the hindquarters of young rapidly growing lambs. This is associated with an apparent increase in sensitivity to insulin, presumably reflecting a change occurring predominantly in skeletal muscle. The extent to which the stimulation of skeletal muscle growth by cimaterol is dependent upon these changes, or the observed increase in plasma somatotropin concentration requires further investiga-
The increase in blood flow and nutrient availability to skeletal muscle, a shift toward different relative proportions of substrate utilization, the possibility of decreased muscle protein degradation and increased protein synthesis and specific receptor-mediated mechanisms may all be involved in the enhancement of skeletal muscle growth by β-adrenergic agonists. Further work is required to clearly define the contributions from each.

References


