Recent Advances in Nutritional Sciences

The Biology of Somatotropin in Adipose Tissue Growth and Nutrient Partitioning

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ABSTRACT During the past 20 years, much has been learned about how porcine somatotropin (pST) affects growth and nutrient partitioning in growing pigs. The development of techniques to produce large quantities of recombinantly derived pST enabled numerous long-term studies to be conducted in which the effects of daily pST administration could be evaluated. Collectively, these studies established that treatment of growing pigs with pST markedly stimulated muscle growth and, concurrently, reduced fat deposition. In growing pigs, maximally effective doses of pST increase average daily gain as much as 10–20%, improve feed efficiency 15–30%, decrease adipose tissue mass and lipid accretion rates by as much as 50–80% and concurrently increase protein deposition by 50%. These effects are associated with a decrease in feed intake of ~10–15%. These responses occur because pST has a wide array of biological effects that modulate nutrient partitioning between adipose tissue and skeletal muscle. The decrease in adipose tissue growth is due to a reduction in lipogenesis that is the consequence of pST blunting the effects of many insulin-dependent events. With respect to fatty acid synthase (FAS), a pace-setting enzyme in the lipogenic pathway, enzyme activity is markedly reduced by pST. This is the result of a pST-mediated decrease in FAS mRNA levels that occurs because FAS gene transcription is decreased. The consequence of the decrease in lipid synthesis is that adipocyte hypertrophy is impaired and, hence, tissue growth. This review will provide an overview of some of the biological effects of pST in adipose tissue and will discuss what is known about the underlying mechanisms that account for these effects. J. Nutr. 130: 2623–2625, 2000.

During the past 20 years, much has been learned about how porcine somatotropin (pST) increases the growth of pigs and the underlying biological mechanisms. These advances were facilitated by the development of methods to produce recombinantly derived pST on a large scale. The availability of large quantities of recombinant pST enabled landmark studies to be conducted that evaluated how administration of pST affected muscle and adipose tissue growth. Administration of pST to growing pigs can increase muscle growth by as much as 50% and concurrently decrease adipose tissue accretion (maximal effect ~70%). The remarkable effects of pST are due to an impressive array of biological effects of the hormone on nutrient utilization, nutrient partitioning and the underlying biological processes that regulate and coordinate these metabolic events in a variety of tissues. One of the hallmark metabolic effects of pST in adipose tissue is that it decreases lipid synthesis and compromises many of the effects of insulin (1–3). Several excellent in-depth reviews have been written about the biological effects of pST on growth and nutrient partitioning and how insulin action is compromised in the pig. Consequently, this review provides an overview of the major findings relative to growth and adipose tissue metabolism; the reader is referred to more extensive reviews for in-depth information about the efficacy of pST and what is known about the biological mechanisms that mediate the effects of the hormone (1–3).

Somatotropin and Growth. Somatotropin (ST) has impressive effects on growth and nutrient partitioning between muscle and adipose tissue. The extent to which this occurs is illustrated by studies in which maximally effective doses of pST (33% and protein deposition (muscle growth) is increased by as much as 62% (reviewed in 2,4). The anabolic effects of pST in muscle contrast with the precipitous decrease that occurs in adipose tissue growth. As shown in Table 1, lipid accretion rates are decreased by as much as 70%. Similar effects of human ST administration were observed in growing children (prepubertal boys) after treatment for 6 mo, albeit the effects were smaller (10% reduction in body fat), likely because of the dose administered (5).

It is important to appreciate that adipose tissue growth in pigs is highly dependent on lipogenic rate and that glucose is the primary carbon source. Isotope kinetic studies have shown that >40% of whole-body glucose turnover can be used by adipose tissue for de novo lipogenesis in 80-kg pigs (6). Thus, any metabolic modifier such as pST, which decreases glucose uptake by adipose tissue, creates a physiologic state in which the tissue is deprived of the primary substrate necessary for lipid accretion. This metabolic adaptation is important for the following reasons: 1) it results in a decrease in the rate of adipocyte hypertrophy and, hence, the rate of adipose tissue accretion; and 2) it accounts for the effects that pST has on productive efficiency and contributes to the increase in muscle growth. In concert with the dramatic shifts in adipose tissue glucose metabolism, glucose that is normally used for lipogenesis is redirected to other tissues, primarily muscle.

Effects of Somatotropin on Adipose Tissue Growth. Lipogenesis. The range of biological effects of pST are extraordinary and have been discussed previously (2). Somatotropin orchestrates many diverse physiologic processes so that more nutrients can be used for lean tissue accretion, and fewer, primarily glucose, are used by adipose tissue. Because the majority (~80%) of lipid in the body is derived from de novo fatty acid synthesis (7) and adipose tissue is the major site of fatty acid

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1 Manuscript received 9 May 2000.

2 Abbreviations used: FAS, fatty acid synthase; IRE, insulin response element; pST, porcine somatotropin; ST, somatotropin; USF, upstream stimulatory factor.

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Effects of pST on the insulin signal pathway(s) to antagonize the postreceptor events that mediate the effects of insulin in the adipocyte are not diminished by ST treatment (18). This is consistent with the fact that some effects in the adipocyte are not diminished by ST treatment (e.g., insulin inhibition of lipolysis; see 2). Little is known, however, about the postreceptor events that mediate the effects of pST on the insulin signal pathway(s) to antagonize the stimulatory effect of insulin on expression of lipogenic enzyme genes. For this reason, studies have been undertaken to use FAS as a model to learn more about how ST regulates FAS enzyme activity and gene transcription. An important rationale for selecting FAS as a model to study was based on the observations that pST markedly reduces FAS enzyme activity (see Table 2) and that enzyme activity and FAS gene expression are exquisitely sensitive to insulin (i.e., insulin increases enzyme activity and gene expression). In addition, the FAS gene is useful to study because changes in enzyme activity are the result of changes in enzyme protein mass that reflect changes in FAS mRNA abundance (reviewed in 19).

On the basis of the evidence that pST decreases FAS enzyme activity (18,20) and the fact that changes in enzyme protein levels reflect changes in FAS protein abundance, it is not surprising that treatment of growing pigs with pST dramatically decreases adipose tissue FAS mRNA levels (21). In addition, in both rat liver and cultured 3T3-F442A adipocytes, ST reduces FAS mRNA abundance and the ability of insulin to increase mRNA, effects that are the result of a decreased transcription (22,23). Somatotropin also shortens the half-life of FAS mRNA from 35 to 11 h (23). Thus, ST reduces FAS mRNA abundance both at the transcriptional level as well as by destabilizing FAS mRNA.

Little is known about how ST affects the insulin signal pathways that blunt the stimulatory effects of insulin on FAS gene expression. Clearly, the effect has to be postreceptor because insulin binding is unaffected. With respect to how ST might interfere with insulin signaling at the distal end of the signal pathway (i.e., at the level of FAS gene transcription), it is probable that this reflects the presence of a somatotropin response element that acts as a negative control element or that ST affects the abundance or binding of a trans-acting factor(s) that interacts with the insulin response element (IRE) in the FAS gene in a way that blunts insulin regulation. Relative to the latter hypothesis, there is an IRE located in the proximal region (from −71 to −50) of the FAS promoter that appears to mediate the stimulatory effect of insulin on FAS gene transcription (24). In this IRE, there is an E-box.

### TABLE 1

<table>
<thead>
<tr>
<th>Study1</th>
<th>Duration</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyd and Bauman, 1989 (1)</td>
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<td>300</td>
</tr>
<tr>
<td>30</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

1 Values in column are pST dose administered [μg/kg body weight] (d).

### TABLE 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>pST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magri et al. (18)</td>
<td>Fatty acid synthase</td>
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</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase</td>
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<td>80</td>
</tr>
<tr>
<td>6-Phosphogluconate dehydrogenase</td>
<td>117</td>
<td>105</td>
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<tr>
<td>Malic enzyme</td>
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<td>66</td>
</tr>
<tr>
<td>Harris et al. (20)</td>
<td>Acetyl-CoA carboxylase</td>
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<tr>
<td>Fatty acid synthase</td>
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<td>9</td>
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<tr>
<td>Glucose-6-phosphate dehydrogenase</td>
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<td>67</td>
</tr>
<tr>
<td>6-Phosphogluconate dehydrogenase</td>
<td>160</td>
<td>84</td>
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<tr>
<td>Malic enzyme</td>
<td>303</td>
<td>184</td>
</tr>
<tr>
<td>Liu et al. (28)</td>
<td>Acetyl-CoA carboxylase</td>
<td>2.0</td>
</tr>
</tbody>
</table>

1 The data presented are expressed in different units depending upon the study. The reader should look at the original papers for further details.
DNA binding motif (5’-CANNTG-3’) for basic-helix-loop-helix transcription factors such as upstream stimulatory factors (USF); both USF1 and USF2 have been shown to bind to this site (25). A study reported that USF binding to the E-box at −65 was required for insulin regulation of the FAS promoter (26). However, it is uncertain whether USF1 mediates the insulin antagonistic effect of ST on FAS gene expression. Studies we have conducted (Yin, D., and Etherton, T. D., unpublished data) demonstrated that neither insulin nor ST affect the abundance of USF1 or binding of USF1 to the FAS-IRE in vitro in 3T3-F442A adipocytes. Thus, our findings indicate that USF1 is not involved in mediating the effects of insulin and ST on the regulation of FAS gene transcription, suggesting that other mechanisms exist. The nature of these mechanisms is not clear and much work remains to be done to clarify how pST decreases FAS gene transcription.

The evidence to date clearly indicates that pST has potent effects on a number of key metabolic events that control adipose tissue growth. The mechanisms by which pST affects nutrient utilization in adipose tissue involve tissue-specific changes in key metabolic pathways as well as alterations in tissue responsiveness to insulin. In many cases, the cellular sites of the alterations in metabolic pathways and signal transduction have been identified, and it is clear that the biological effects of pST are dependent upon multiple changes. This metabolic regulation occurs in an orchestrated manner that results in the redirection of glucose away from lipid synthesis to muscle to provide additional ATP to support the increase in muscle protein deposition that occurs. The consequence of a decrease in lipid synthesis is that adipose tissue growth is dramatically reduced. At the gene level, we have much to learn about how pST blunts the effects of insulin on FAS gene transcription. The diverse spectrum of effects of pST in a variety of tissues as well as in a specific tissue reinforces the fact that multiple intracellular signaling events likely mediate the effects of the hormone. The nature of these signal pathways is obscure; with respect to adipose tissue, much remains to be unraveled about the mechanisms that account for the precipitous decrease in tissue growth. Nonetheless, it is evident that pST plays a key role in regulating adipose tissue metabolism. As we learn more about the mechanisms by which pST blunts adipose tissue growth, it is not unreasonable to speculate that we may discover innovative strategies that can be implemented clinically for the prevention and treatment of human obesity. The large body of evidence from studies conducted with growing pigs treated with pST provides compelling support for the idea that with respect to adipose tissue, ST is not a “growth” hormone; rather, it is a potent metabolic hormone that has remarkable antiobesity effects.

**LITERATURE CITED**


