Altering Growth in Swine by Manipulating the Somatotropin Status — Review of Emerging Technologies

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Introduction

The mission of animal science research is to provide biological and management "tools" to animal agriculture which facilitate efficient animal production and product acceptability. Productive efficiency of growing swine is determined by the proportion of nutrients partitioned to fat relative to muscle and by the rate at which tissue accretion occurs. Acceptability of the meat product is markedly influenced by fat content. A recent report from the National Research Council (1988) cites the recommendations of both medical and health professionals who urge reduced consumption of dietary fat; particularly that of animal origin. Furthermore, consumers are becoming more health conscious with a growing preference for leaner meat. Present efforts by animal scientists in the area of growth regulation are timely indeed. By attempting to alter the rate and composition of gain, we simultaneously address the issues of productive efficiency and product acceptability.

Techniques for altering the balance between lean and adipose tissue growth in swine have previously involved genetic selection and employment of a variety of management strategies (e.g., intact males, limit feeding, lower slaughter weights). Recent advances in recombinant DNA technology are giving rise to a technological revolution that will permit animal scientists to employ new 'tools' which dramatically alter growth and development. For example, we now have the ability to produce recombinant products such as somatotropin (ST) which exhibit regulatory effects on metabolism during postnatal growth. Administration of ST to young growing swine has yielded unprecedented results with respect to the rate, efficiency and composition of gain (Evock et al., 1988; Campbell et al., 1988; Boyd and Bauman, 1988). These achievements would normally have required 10 to 20 years of intense genetic selection (Table 1).

Relative Responses to Somatotropin — Benchmarks in Performance

The data in Table 1 show the estimated rate of progress achievable through a genetic selection program. The paper by Mitchell and co-workers (1982) was selected for presentation because the selection objectives and criteria for simultaneous emphasis were most relevant to the needs of commercial swine production. The response to ST affirms that considerable time would be required for similar changes to be achieved by selection alone. Further, genetic capacity is far greater than is presently expressed in the growing pig and circulating levels of ST are clearly a limit to expression of growth potential. Its administration should be considered as an adjunct to genetic selection. Even highly selected strains exhibit a marked response to pST (Campbell and Taverner, 1988) since performance 'maxima' are not yet evident for criteria cited (Table 1).

Although the observed responses to ST (as shown in Table 1) are dramatic, they are nevertheless conservative. We now appreciate that the ST response is a function of diet adequacy and that increases in the order of 25% to 40% are achievable for rate and efficiency of gain. We published theoretical estimates of the amino acid requirements for growing swine (50-100 kg) in a recent report (Boyd et al., 1988b). These served as the basis for subsequent studies in which greater relative responses were observed. We assumed an amino acid requirement appropriate for accretion of 300 grams of protein per day in highly selected strains of swine. This should ensure that the ST response is not constrained by nutrient input. The theoretical estimates assume that the efficiency of absorbed nitrogen use is not altered, given the lack of appropriate data.

The absolute levels of performance are not evident from Table 1; however, a minimal statement is warranted. Rates of whole body protein accretion in the order of 220-240 grams/day (vs 110-130) have been achieved in male castrates and females (50-100 kg), while lipid accretion rates were reduced to approximately 30-50 grams/day (300-350). This alteration in the pattern of the major components of gain resulted in impressive 'benchmarks' for both rate (1130-1230 grams/d) and efficiency (2.0-2.1) of gain (Boyd and Krick, unpublished data). The potential difference in dissectable lean tissue yield at 100 kg is approximately 9 kg (Thiel et al., 1989). When intact males (60-90 kg) from a herd selected for both lean tissue growth and feed conversion were treated with ST, protein accretion rates of 250-280 grams/day were observed. The rate and efficiency of live weight gain was approximately 1500-1550 grams/day and 1.7-1.9 respectively (Campbell and Taverner, 1988). It is important to appreciate that the levels of performance achieved in practice depend on the genotype and blood levels of ST obtained by the delivery system.

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Table 1. Comparison of Relative Responses to Genetic Selection and Somatotropin Administration.

Item	Genetic Selection[a]		Somatotropin[b]	
	Absolute Change per Generation	% Change	Absolute Change	% Change
Daily gain, g/d	+ 5.0	+0.7	+100	+10.5
Feed: gain, units	− .03	−1.0	−.87	−28.5
Daily intake, g/d	− 7.3	−0.4	−590	−20.3
Lean gain, g/d	+ 6.0	+2.1	ND	—
Feed: lean gain	− .17	−2.4	ND	—
Loin eye area, mm²	+27	+0.8	+449	+13.1
Backfat depth, mm	− 1.8[c]	−5.5	− 7	−25.0
Carcass protein, g/d	ND	—	+ 54	+54.0
Carcass lipid, g/d	ND	—	−204	−69.0

[a] Data from Meat & Livestock Commission (1970-1977), Mitchell et al., 1982.
[b] Boyd et al., 1986; Boyd and Bauman, 1988 (120 ug ST/kg BW).
[c] Cleveland et al., 1982 (5 generations of selection).

Control of Somatotropin Secretion

Somatotropin is a protein secreted by the anterior pituitary gland. The controls of ST secretion and pST's direct and indirect involvement in tissue metabolism is portrayed in Figure 1. Since exogenous administration of ST enhances the rate and composition of growth, any strategy that increases blood concentrations of ST would potentially be a feasible approach for manipulating animal growth. For example, manipulation of endogenous ST secretion can occur by over-riding the inhibitory effects of somatostatin or by increasing the secretory stimulant – growth hormone releasing factor (GRF). Also, one component of the ST response is an increase in the concentration of insulin-like growth factor 1 (IGF-1). Since IGF-1 appears to mediate many of the effects ascribed to ST, it has been considered a possible target for manipulation.

Given the technologies which presently exist and our understanding of the biology, there are at least 5 targets or approaches to manipulation of the ST 'pathway':

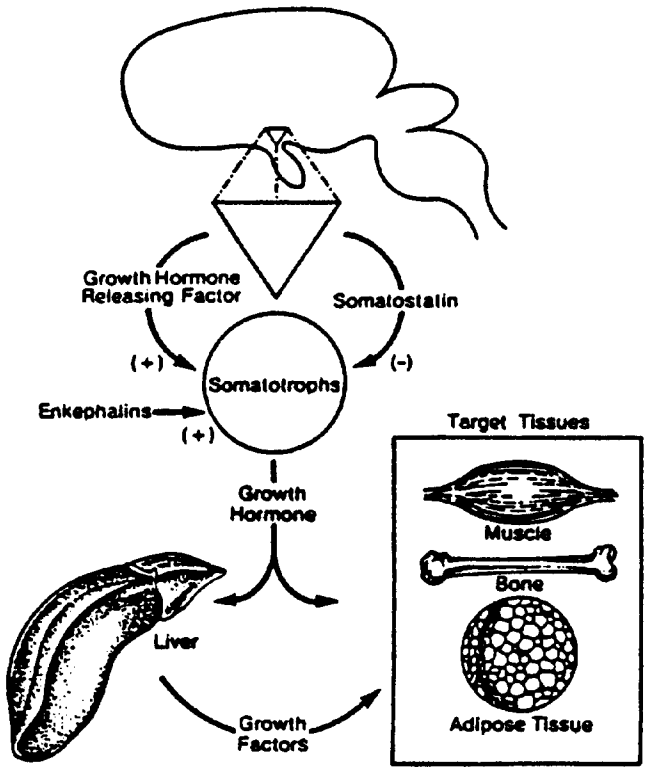
1. Exogenous ST.
2. Exogenous GRF or other ST secretogues.
3. Insulin-like growth factor – 1.
4. Immunological manipulation of ST secretion or potency.
5. Gene Insertion (ST, GRF).

Pharmacological alternatives also exist and are under investigation (e.g., repartitioning agents, such as B-adrenergic agonists). A discussion of these is beyond the scope of this paper. We intend to confine our discussion to those techniques associated with the ST axis and which are under serious and systematic investigation.

Exogenous Somatotropin

Somatotropin appears to be a family of peptides with the major component being a 22 kDa form consisting of 191 amino acid residues. A recent paper from our laboratory demonstrates that the potency of ST can be increased by structural modification of the ST molecule. We compared the biological activity of a novel recombinantly derived 21 kDa variant of porcine ST to the 22 kDa form (Boyd et al., 1988a). This variant is missing a deletion peptide (amino acids 32-38). In preliminary experiments with heterologous models, the variant form of ST exhibited substantially greater activity as determined by rat liver membrane receptor binding and the hypophysectomized rat growth bioassay systems (K.D. Fagin, Personal Communication). The variant also exhibited significantly greater nutrient partitioning activity in swine, with improvements in compositional gain (lipid, protein) and in the

Figure 1



Regulation of Somatotropin (ST) synthesis and secretion is determined by the hypothalamic hormones, ST releasing factor (GRF - stimulatory) and somatostatin (inhibitory). The somatotrophs may also respond to other secretogues (Figure from Convey, 1987).

efficiency of growth. A parallel example is cited below for GRF in which the potency was markedly improved (10-fold) by structural alteration.

The limiting step in administering ST to farm animals is in the development of a suitable delivery system. ST must be administered in a vehicle that provides controlled releases over a sustained period of time (e.g., 30 days). It is difficult to assess the progress in this area since much of the research is occurring within the private industry sector. Encouraging reports have been published recently by researchers from Monsanto Company (Knight et al., 1988) and by Wang and Kothe (1988).

Alternative strategies to ST administration may be sought for reasons other than administration mode and cost effectiveness. For example, exogenous administration represents to some a hormone approach to animal production. Even if concerns of safety to animal and consumer are completely satisfied by regulatory agencies, approaches appearing to be more natural (e.g., immunological route) may in some cases prove to be publicly more acceptable. This may be especially true for some European countries.

Somatotropin Releasing Factor and Releasing Peptides

As shown in Figure 1, ST secretion is regulated by 2 hypothalamic neuropeptides – GRF and somatostatin. GRF is a potent and specific stimulant of ST release. In the short times since the isolation and characterization of human GRF (hGRF; Guillemin et al., 1982; Rivier et al., 1982), it has proven to be an effective treatment for ST-deficient children (Gelato et al., 1984; Thorner et al., 1985). It has potential application in farm animal species for performance enhancement. There is considerable sequence homology between hGRF (1-44) - NH_2 and that isolated from several animal species. This is particularly true for the first 29 amino acid residues from the NH_2 terminus (Schanbacher, 1986). Structure-activity studies have shown that full activity lies within this region. Porcine GRF is identical to hGRF in the 1-29 amino acid region, hence the expectation that hGRF or expression of the hGRF gene might elicit biological activity in swine similar to porcine GRF.

GRF increases serum ST concentrations in a dose-dependent manner in humans and in a number of farm animal species (Schanbacher, 1986; Convey, 1987) including swine (Kraft et al., 1984; Etherton et al., 1986; Johnson et al., 1988). There are few published studies, however, on the effects of long-term administration of GRF on growth performance in swine or meat animals in general. Early attempts to investigate the effect of GRF administration involved intermittent injections. This was due to evidence in rats which suggested that a pulsatile pattern of administration (versus continuous infusion) was necessary to cause ST release (Clark & Robinson, 1985; Jansson et al., 1982). However, studies with GRF given either in multiple injections or as a continuous infusion have yielded equivalent increases in nitrogen retention in growing calves (Moseley et al., 1987) and in milk production for dairy cows (Enright et al., 1986) and ewes (Hart et al., 1985). This observation dispelled early concerns that pituitary somatotrophs may become refractory to continuous GRF exposure and suggests that GRF or other ST releasing peptides are viable targets for promoting growth.

Recently, a series of studies was conducted with growing swine using a novel and potent analogue of hGRF (1-29) (Heimer et al., 1988). These studies demonstrate the potential for a GRF-mediated route of growth promotion and show the merit of using structural modification to enhance biological activity. Scientists at Hoffman-La Roche altered the biologically active region of hGRF by the substitution of 3 amino acids. The molecular basis for the structural modification and evaluation for activity are published in a paper by Heimer and co-workers (1988). The tri-substituted GRF (des-NH_2 Tyr_1, D-Ala_2, Ala_{15} [GRF 1-29 NH_2]) exhibited greater potency in swine than the 1-44 hGRF construct (approximately 10 fold). The increase in potency was attributed to the enhanced stability of the NH_2-terminus to enzymatic degradation by a plasma diaminopeptidase. This enzyme degrades GRF by metabolizing GRF(1-44)-NH_2 to GRF(3-44)-NH_2. Since the structurally modified GRF is a poor substrate for the diaminopeptidase, its clearance rate is considerably slower than observed for the parent compound.

Following a study to determine the optimum dose and periodicity of injection (Pelletier et al., 1988), Canadian scientists administered this analogue to growing swine (6.7 ug/kg BW 3 times daily) to determine the effects on growth performance and carcass characteristics (Pommier et al., 1988; Dubreuil et al., 1988). The results were similar, in magnitude, to those achieved when ST is administered exogenously (Table 2). It is noteworthy that the dose of GRF analogue required to elicit dramatic changes in performance and composition of gain is relatively low. This and the fact that the peptide is relatively small are attractive features for potential commercialization.

Other approaches to stimulation of endogenous secretion of ST include small somatotropin-releasing peptides such as an enkephalin analog, Tyr-D-TR-Gly-Phe-Met-NH_2 (Bowers et al., 1981). This peptide is also specific for ST secretion. Another compound of this series (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2) has been shown to increase serum ST concentration in growing swine (Doscher et al., 1984) and cattle (Kraft et al., 1984), but we are not aware of any demonstrated effects on performance of farm animals by either of these ST-releasing peptides.

Mediation of Somatotropin Effects – IGF 1

Another possible way to elicit the ST response is via a down-stream approach – administering factors which mediate the ST response. One component of the ST response is an increase in IGF-1 (somatomedin-c) concentrations. Since many of the growth-promoting effects observed with ST administration are thought to be mediated by these elevated levels of IGF-1, it is reasonable to speculate that direct administration may enhance growth performance. The most direct evidence for the somatomedin hypothesis is that IGF-1 can stimulate growth in rats. Several researchers have reported increases in growth indices when hypophysectomized rats (Schoenle et al., 1982; Schoenle et al., 1985; Skottner et al., 1987; Guler, 1988) and normal rats (Hizuka et al., 1986) received infusions of IGF-1. In general, the growth response elicited by direct administration of IGF-1 has not been as

Table 2. Effect of a Potent Analog of hGRF (1-29) on Growth Performance and Carcass Characteristics of Growing Swine.[a]

Item		*Saline*	*hGRF[b]*	*SE*	*% Difference*
No. Swine		16	16	—	—
Gain,	kg/d	1.06	1.12[c]	.02	+ 5.7
Feed/Gain		2.97	2.38[c]	.07	−19.9
Feed Intake,	kg/d	3.01	2.57[c]	.03	−14.6
Loin area,	cm^2	34.1	38.4 [c]	.8	+12.6
Backfat,	mm	27.1	19.5 [c]	1.0	−28.0
Dissected:	*Number*	8	8	—	—
Ham					
- Muscle	kg	5.35	6.05[c]	.16	+13.1
- Fat	kg	2.65	1.94[c]	.14	−26.8
- Bone	kg	.92	1.03[c]	.04	+12.0
Shoulder					
- Muscle	kg	5.69	6.61[c]	.15	+16.2
- Fat	kg	2.70	2.34[c]	.14	−26.5
- Bone	kg	1.36	1.72[c]	.03	+13.3

[a] Dubreuil et al., 1988 & Pommier et al., 1988. Selected trts. Start wt. 49 kg; End wt. 106 kg.

[b] Desamino - Tyr^1 – Ala^2...Ala^{15} – hGRF(1-29)NH_2 Analog. Injected 3 times daily.

[c] $P<.05$.

great as that observed with ST. In many of these studies, the blood levels of IGF-1 achieved by infusion were not as high as those achieved with ST administration even though the amount of IGF-1 infused was quite large. This may account for the reduced response. Most experiments designed to study the effects of IGF-1 on various tissues have been performed in vitro and often using supra-physiological concentrations of IGF-1; many of the effects observed in such studies may be due to IGF-1 binding to the insulin receptor. To date, there has not been enough IGF-1 available to study the in vivo effects of long-term administration of exogenous IGF-1 in farm animals.

In swine, somatotropin treatment results in an elevation of IGF-1 levels (Chung et al., 1985; Etherton et al., 1987; Campbell et al., 1988; Evock et al., 1988). Low levels of IGF-1 have been observed in small breeds of dogs (toy poodles; Eigermann, 1985) and swine (minipigs; Buonomo et al., 1987), although levels of ST were normal. Elevation of circulating IGF-1 levels may be necessary for the expression of ST's effects on growth performance. However, IGF-1 may not be an effective growth promoter without the interaction with ST. ST may modulate some of the effects of IGF-1 on target tissues – either directly or via induction of the 150 kDa binding protein (Zapf and Froesch, 1986). Walton et al. (1987a,b) demonstrated that pST suppresses insulin- and IGF-1-stimulated lipogenesis and that the 150 kDa binding protein can block the IGF-1 insulin-like lipogenic response in porcine adipose tissue.

The large (150 kDa) IGF binding protein is ST-dependent, while the small (40 kDa) IGF binding protein appears to be ST-independent. When ST is administered, the large binding protein increases in concentration along with IGF-1 (Etherton 1989; Zapf and Froesch, 1986; Buonomo et al., 1987); the concentration of this binding protein is greatly depressed in hypophysectomized swine (Buonomo et al., 1987). The large binding protein thus may be playing an important role in the regulation of IGF-1 function. For instance, the binding proteins could be maintaining IGF-1 levels in the blood stream, allowing their effects to be sustained. Or perhaps the large binding protein could inactivate locally produced IGF-1 by binding and transporting it to catabolic sites. Its affinity for IGF-1 is quite high and the half-life of IGF-1 is greatly increased when bound. When IGF-1 is infused into rats, very little of the free form is detectible. While a single bolus of IGF-1 disappears rapidly, a constant infusion of IGF-1 in rats seems to allow the IGF-1 to equilibrate with the binding protein, allowing blood levels to rise (Zapf et al., 1985). However, a constant infusion of IGF-1 in lactating cows does not result in an elevation of blood IGF-1 (Plaut et al., 1988) and free IGF-1 injected into swine disappears rapidly (Etherton, 1989). The binding proteins in both cases appear to be saturated.

Although IGF-1 infusion has been shown to reproduce many of the effects of ST administration, much more IGF-1 is required to achieve the same level of response as ST. On a molar basis, ST is 10- to 15-fold more potent than IGF-1 (Clemmons et al., 1987). Structurally modified forms of IGF-1 which are more potent than the native compound have now been produced (Cascieri et al., 1988). However, other problems with IGF-1 as a growth promoter exist. It is not clear what the active form of IGF-1 is in vivo (bound vs free). Unbound IGF-1 mimics insulin, stimulating lipogenesis and causing hypoglycemia in pigs (Etherton, 1989); neither is desirable in meat-producing animals. It is uncertain whether or not binding protein synthesis would be induced with IGF-1 administration; and without its presence (or that of ST), the insulin-like effects of IGF-1 would ensue. Although Guler et al. (1988) reported that the epididymal fat pad was decreased in hypophysectomized rats treated with IGF-1, it appears that the decreased adipose accretion rates observed in ST-treated pigs are a direct effect of ST (Boyd & Bauman, 1988). Local production of IGF-1 (stimulated by ST) may be more important than circulating IGF-1 levels. Such a scenario would mean that only a transgenic approach – insertion of the IGF-1 gene and possibly that of the binding protein into the genome of farm animals – would be likely to succeed.

At least two problems must be seriously considered when

discussing IGF-1 as an alternative to ST for growth promotion. First, it is unclear whether IGF-1 is capable of orchestrating the diverse effects on tissue metabolism ascribed to ST. Particularly important may be the direct effects ST seems to have on bone and adipose (Boyd & Bauman, 1988). Second, it is possible that any technique which does not increase production of the binding protein in conjunction with elevation of IGF-1 may not be effective. The roles of ST, binding proteins and local IGF-1 production in the regulation of IGF-1 must be more completely understood before the application of direct administration of IGF-1 can be considered commercially as a means of achieving the ST response.

Immunological Intervention

The recent ban by the European Economic Community (EEC) on hormone-based growth promotants has focused attention on alternatives to exogenous hormone administration. Immunological manipulation of specific endocrine events is an attractive alternative since it may be perceived as a more natural means of promoting growth. Certain immunological approaches appear to improve the efficiency of ST use or mimic its action. This suggests possible advantages in the cost-benefit relationship. Strategies presently under investigation include (1) active immunization against somatostatin to increase ST secretion, (2) use of monoclonal antibodies with specific antigenic determinants to increase biological activity of ST and, (3) use of 'surrogate' molecules to mimic the ST effect.

Somatostatin, which is the counter-regulatory peptide of ST secretion, inhibits ST release, (Fig. 1). Neutralization of somatostatin was conceived early in the search for alternatives to ST administration. Attempts to alleviate the effects of somatostatin by immunization have resulted in mixed results to date with respect to plasma ST concentration and growth enhancement in ruminants (Schanbacher, 1986; Shelling & Byers, 1988). We are not aware of any definitive report on somatostatin immunization in swine; however, given the relative response of swine to ST, this might be the more sensitive species. Nevertheless, failure to achieve more consistent and dramatic results in growing sheep and cattle, in addition to a lack of specificity for ST (e.g., inhibits at least 8 other hormones), seem to make this a less likely target for manipulation.

A novel and intriguing biological phenomenon results when specific monoclonal antibodies (Mab) interact with ST. Mab have been shown to enhance the effectiveness of hST with respect to the rate, efficiency and composition of gain in dwarf mice (Aston et al., 1986; Holder & Aston, 1989). This find is unequivocal, nevertheless unexpected since binding of antibodies to hormones generally inhibits hormone activity. At the present time, the mechanism of Mab-mediated enhancement of ST action is speculative.

Pell and co-workers (1988) were the first report to test the possibility of Mab-enhanced ST action in farm animals. They observed that Mab, with specific antigenic determinants, increased milk production of lactating ewes treated with bST, above the increase elicited by bST alone. We are not aware of any report on the effects of Mab on growth and composition in meat animals. However, the forementioned results provide incentive for further pursuit of this route to improve the efficiency of ST use by farm animals.

Another immunological strategy for manipulation of growth is to use the immune system's anti-idiotype network to produce antibodies which structurally resemble ST and which are capable of mimicking its action (Hannah report, 1986; Flint, 1987). Such antibodies (or hormone images) have been raised to rat and ovine ST. They effectively compete with ST for liver and adipose receptors of the respective species (Hannah report, 1986). Hypophysectomized rats have responsed with an increase in body weight gain similar to that observed with ST administration. Although we are not aware of any report demonstrating this to be a feasible approach for ST enhancement of growth in meat animals, this is a conceptual possibility worthy of careful consideration. An attractive feature of this and other immune approaches is the induction of antibodies in high concentrations which would be expected to circulate in the bloodstream for prolonged periods without further treatment. However, this may be seen as a disadvantage in some cases.

Transgenic Technology

The emergence of recombinant genetic technology and embryo manipulation have provided the facility for controlled genetic alteration of the genome via gene insertion. Significant developments in biology are still required, however, before this tool for increasing endogenous production of ST can be commercialized. This technology integrates sophisticated approaches from a number of fields of investigation and represents another alternative to administration of peptide hormones.

Rat (Palmiter et al., 1982) and human (Palmiter et al., 1983) structural genes, ligated to a metallothionein-I (MT) promoter or regulatory region, were introduced into mice via micro-injection of fertilized eggs. Mice that incorporated and expressed the foreign gene produced large quantities of ST and grew more rapidly than littermate controls. Similarly, the MT-hGRF gene clone has also been introduced into mice. Those expressing the gene had elevated ST levels, resulting in marked increases in weight gain relative to littermate controls (Hammer et al., 1985a). In neither instance, unfortunately, was the composition of gain determined. This information is essential for determining the effectiveness of a growth promoter in meat animals.

Recently, genes coding for ST and GRF have been inserted into the genome of farm animals via micro-injection into the pronucleus or nucleus of fertilized ova. The first report of transgenesis in swine involved insertion of the structural gene for hST with a MT-I promoter region (Hammer et al., 1985b). Since then, structural clones for the gene of bovine (Pursel et al., 1987; Wieghart et al., 1988) and rat (Ebert et al., 1988) ST have been inserted into the genome as has that for hGRF (Pursel - personal communication). With the exception of a recent paper by Vize and co-workers (1988), the gene construct cloned for insertion has been non-porcine. Despite the enormous effort to produce swine with enhanced ability for ST secretion, only one study has had sufficient littermates to document the potential for improved growth and carcass composition of transgenic pigs (Pursel et al., 1988a; Table 3).

Table 3. Growth Potential of Metallothionein-bST Transgenic Swine Fed Ad Libitum from 30 to 90 kg Body Weight[a].

Period	*Treatment*	*No./Trt*	*Gain, g/d*	*Intake, kg/d*	*Feed:Gain*
30-60 Kg	Control	8	761 ± 35	2.08 ± .05	2.77 ± .14
	Transgenic	4	988 ± 44[b]	2.12 ± .07	2.21 ± .17[b]
	% Difference	—	+30%	ND	−20%
60-90 Kg	Control	7	884 ± 28	2.93 ± .11	3.33 ± .18
	Transgenic	3	948 ± 38	2.39 ± .15[b]	2.58 ± .25[b]
	% Difference	—	+ 7%	−18%	−22%

[a] Pursel et al., 1988a and personal communication. Diet contained 18% CP with .25% Lysine. Eight pigs allocated per treatment with disproportionate numbers of transgenic pigs due to health problems.
[b] $P<.05$.

The results presented in Table 3 clearly demonstrate that enhanced rate and efficiency of gain may be achieved in swine with insertion of the ST gene. In accordance with studies using exogenous ST treatment, subcutaneous fat was dramatically decreased, thereby implying increased lean mass. Ultrasonic estimates of backfat thickness (10th rib, approximately 90 kg) were 20.5 mm and 7.9 mm for control and MT-bST pigs, respectively (Pursel et al., 1989). However, this is a slight overestimate of the actual backfat thickness since skin thickness over the respective rib was approximately 1 mm thicker than in the littermate controls. Although transgenic pigs grew more rapidly and efficiently, they also exhibited a number of adverse effects. These included lameness, ulcers, lethargy and suspectibility to stress; hence, the disproportionate number of animals actually completing the study as noted in Table 3. These adverse effects are believed to be caused by prolonged exposure to the pharmacological levels of plasma ST expressed by most of the transgenics studied thus far by Pursel and co-workers.

The remarkable accomplishments of transgenesis must not over-shadow the fact that critical biological questions must be addressed before application to farm animals can be truly successful. First, the basic mechanisms responsible for regulation of gene expression in mammalian cells are not yet understood. There are several levels of gene control, hence different control elements may exist. This facet is discussed in a review by Wagner and Jochle (1986). Second, the process of insertion into the genome of the germ-line is largely random. At present, there is generalized incorporation across tissues and uncertainty relative to the determination of gene placement and integrity of associated genomic sequences (i.e., those on either side). Finally, the specific approach to transgenesis will undoubtedly evolve and have multiple approaches for a given endpoint as we learn more about the biology, recognize specific points of regulation and determine how amenable they are to regulation at the gene level.

Summary

Somatotropin has been shown to exhibit regulatory effects on metabolism. Exogenous administration markedly alters the rate and pattern of tissue growth in swine by directing nutients toward or diverting them from specific tissues in a highly coordinated manner. Strategies that increase the blood concentration of this naturally-occurring polypeptide will provide swine producers with the opportunity to simultaneously effect dramatic changes in production efficiency and to provide consumers with a truly lean food product. Recent innovations in biology are giving rise to new biological "tools" which will permit animal scientists to employ a variety of approaches to achieve the ST response. In the near future (2-5 years), the ST response may be achieved through exogenous ST, appropriate secretogues of ST release, or perhaps by employment of site-specific antibodies which enhance the biological activity of ST. In the long term, it seems conceivable that the ST axis may be manipulated genetically as techniques for genetic improvement evolve to sophisticated and specific methods for controlled gene expression or gene insertion. We anticipate that the possibilities may be of sufficient breadth to satisfy public mandates against the use of certain technologies in meat animal production.

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