Influence of Porcine Somatotropin Administration and Sex on Glucose and Endocrine Responses in Obese Pigs (43790)

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Abstract. **The endocrine and hyperglycemic responses to chronic administration of exogenous porcine somatotropin (pST) were investigated in genetically obese intact and castrate male (boars and barrows) and female (gilts) swine. Somatotropin was administered at a dose of 4 mg·pig^{-1}/day by daily im injection. After a 26-hr fast on Day 22 of treatment, a loading dose of glucose (0.5 g/kg body wt) was administered iv, and blood samples were collected to determine parameters of glucose clearance and responses to a glucose bolus. Blood samples were assayed for glucose, insulin, insulin-like growth factor (IGF)-I, IGF-II, and pST. On Day 24 of treatment, blood samples were similarly collected every 15 min for 8 hr, to examine metabolic and endocrine measures in the fed state. After collection of the 6-hr sample, porcine growth hormone-releasing factor (pGHRF, 0.5 μg/kg body wt) was administered iv. Administration of pST reduced feed consumption, increased gain, and resulted in 50% greater efficiency of gain. Plasma glucose was increased with pST treatment in both fasted (44%) and fed (64%) pigs. After administration of glucose bolus, glucose distribution volume and half-life ($t_{1/2}$) were approximately doubled and MCR was reduced 75% in pST-treated pigs. Peak glucose-induced insulin concentrations were increased in pST-treated gilts and barrows but not boars. Concentrations of IGF-I were increased with pST treatment. Concentrations of pST during the sampling periods were influenced by sex and pST treatment. Control pigs responded to GHRF administration with increased plasma concentrations of pST, whereas, no pST response to GHRF administration was observed in the pST-treated pigs. The glucose and insulin results indicate chronic administration of pST to gilts and barrows induces insulin insensitivity and enhances insulin responses to a glucose challenge. The differences among the sexes in pST concentrations in the pST-treated pigs suggest differences in sexual differentiation or activation of the mechanisms of pST clearance.**

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Chronic administration of somatotropin (ST) increases accretion of lean tissue and decreases accretion of fat. These actions of ST have been investigated in a variety of human conditions characterized by lean tissue wasting or reduced rate of accretion (e.g., ST deficiency, geriatric men, and anorexics infected with HIV [1]), as well as in meat animal production. Rate and efficiency of gain of lean tissue is markedly improved in growing pigs given porcine ST (pST) (2–6). Circulating pST, which is increased by its administration, induces increased serum concentrations of insulin-like growth factor-I (IGF-I), insulin, and glucose, and decreased serum values for urea nitrogen (5, 6). The diabetogenic effect of ST, increase in circulating glucose, has been observed in most mammalian species (7). We have suggested this pST-induced hyperglycemia may be a mediator of the action of pST on growth (5, 6). This increase in serum glucose may be due to decreased utilization of glucose by the peripheral tissues or increased gluconeogenesis (8–11). The evidence is that the glucose regulatory sys-

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tem is altered with pST treatment, however, the metabolic mechanisms involved are uncertain.

Sex or gender has a significant influence on rate, pattern, and efficiency of animal growth, as well as growth response of pigs to exogenous pST (12, 13). There is little available information which allows comparison of the metabolic responses across gender or sex.

The objective of the present study was to quantify responses to chronic administration of pST in measures of glucose metabolism and serum concentrations of growth regulating hormones in male, castrate male, and female swine to gain further understanding of the mechanisms by which exogenous ST alters growth.

Materials and Methods

Genetically obese intact males (boars), castrate males (barrows), and intact females (gilts) used in the study were from *inter se* matings of crossbreeds produced by within-line matings of purebred Duroc and Yorkshire pigs selected solely for high backfat thickness over multiple generations (14). These genetically obese swine are not hyperglycemic, hypertriglyceremic, hypercholesterolemic or hyperinsulinemic (15). However, in response to pST administration these pigs exhibit an amplified hyperglycemic response, a variable of interest in the present study. At the beginning of the study, pigs weighed 46.2 ± 0.6 (mean ± SE) kg body wt. Recombinantly derived porcine somatotropin (pST) was administered daily between 06:30 and 07:30 hr by im injection in the neck over the extensor muscle at a dose of 4.0 mg/d in 1.0 ml 25 m*M* bicarbonate buffer. Control pigs received 1 ml 25 m*M* bicarbonate buffer. The study was a 3 × 2 factorial arrangement of treatments with four pigs per sex-pST cell. During the study, pigs were individually housed in slotted floor pens (1.2 × 1.2 m) in an enclosed, temperature-controlled building with free access to water. Feed was a 19% crude protein corn-soybean meal diet meeting or exceeding suggested NRC requirements (16). Calculated lysine content of the diet was 1.08%. Pigs were given *ad libitum* access to feed for 1 hr twice daily, 06:00–07:00 and 15:00–16:00 hr. Body weights and feed consumption were determined at Day 0, 9, 18, and 25 of the trial.

Pigs were fasted from the morning meal of Day 17 until the afternoon meal of Day 18. The morning of Day 18 the pigs were weighed, and indwelling jugular cannulae were implanted. On Day 21 of the trial, pigs were offered the morning meal. Pigs were then fasted until the afternoon meal of Day 22. On Day 22 pigs were injected with pST at 06:45 hr. At 08:00 hr, blood sampling for examination of glucose tolerance in the basal fasted state was begun. Two blood samples were collected 5–10 min before administration of the glucose load. One sample (10 ml) was collected into an EDTA-treated syringe for measurement of plasma concentrations of pST, IGF-I, IGF-II, and insulin, and the other sample (2.7 ml) was collected into a potassium fluoride-treatment syringe for measurement of plasma glucose concentrations. At Time 0, 50% D-glucose was administered via the cannula at a dose of 0.5 g/kg body wt and the cannula flushed with approximately 5 cannula volumes of 0.9% NaCl. The dose of glucose solution was based on body weight obtained on Day 18. Blood samples were collected at approximately 10, 20, 30, 45, 60, 75, 90, 105, 120, 135, and 150 min after administration of the glucose. Actual times were recorded. At each sampling time, two samples were collected as described above. One control gilt died during cannulation, and a control boar did not provide glucose tolerance data due to a nonfunctioning cannula.

On Day 24, pigs were injected with pST at 06:45 hr and fed the morning meal between 06:30 and 07:30 hr. The afternoon meal was not offered until after collection of the 16:00 hr sample. Blood samples for determination of concentrations of glucose and endocrines

Table I. Least-Squares Means and Analysis of Variance for Measures of Growth Performance of Control and PST (4 mg/d)-Treated Obese Pigs

	n	Feed intake (kg/d)	Gain (kg/d)	Efficiency[a] (gain/feed)
Treatment sex				
Control boar	4	1.6 ± 0.1	0.37 ± 0.06	0.24 ± 0.04
PST boar	4	1.5 ± 0.1	0.54 ± 0.05	0.36 ± 0.04
Control barrow	4	1.8 ± 0.1	0.38 ± 0.05	0.21 ± 0.03
PST barrow	4	1.2 ± 0.1	0.42 ± 0.05	0.33 ± 0.03
Control gilt	3	1.3 ± 0.1	0.24 ± 0.07	0.18 ± 0.04
PST gilt	4	1.1 ± 0.1	0.38 ± 0.05	0.28 ± 0.04
Analysis of variance		Prob > F	Prob > F	Prob > F
Sex		0.09	0.11	0.35
Treatment		0.02	0.02	0.01
Sex*trt		0.08	0.43	0.95

[a] Efficiency = kg body wt gain per kg of feed consumed during 25-day trial.

Table II. Least-Squares Means and Analysis of Variance for Measures Obtained During Glucose Tolerance Test of Fasted Control and PST (4 mg/d)-Treated Obese Pigs

Treatment sex		Glucose					Insulin	
	n	Fast. conc. (mg/dl)	Dist. volume (liter)	$t_{1/2}$[a] (min)	MCR[b] (ml/min)	MCR ([ml/min]/kg$^{.75}$)	Fast conc. (μIU/ml)	Peak conc. (μIU/ml)
Control boar	3	89 ± 5	10 ± 1	17 ± 3	188 ± 17	9.3 ± 0.9	33 ± 18	224 ± 83
PST boar	4	128 ± 5	14 ± 1	35 ± 3	101 ± 17	4.8 ± 0.9	24 ± 18	250 ± 83
Control barrow	4	82 ± 4	7 ± 1	15 ± 3	200 ± 15	10.3 ± 0.8	18 ± 16	136 ± 72
PST barrow	4	118 ± 4	13 ± 1	30 ± 3	119 ± 15	5.9 ± 0.8	18 ± 16	384 ± 72
Control gilt	3	79 ± 4	6 ± 1	20 ± 3	150 ± 15	8.2 ± 0.9	11 ± 18	69 ± 83
PST gilt	4	115 ± 4	13 ± 1	36 ± 3	88 ± 15	4.5 ± 0.8	73 ± 16	448 ± 73
Analysis of variance		Prob > F	Prob > F	Prob > F	Prob > F	Prob > F	Prob > F	Prob > F
Sex		0.08	0.13	0.18	0.06	0.15	0.70	0.97
Treatment		0.01	0.01	0.01	0.01	0.01	0.01	0.01
Sex*trt		0.89	0.56	0.85	0.74	0.89	0.18	0.11

[a] Half-life.
[b] Metabolic clearance rate.

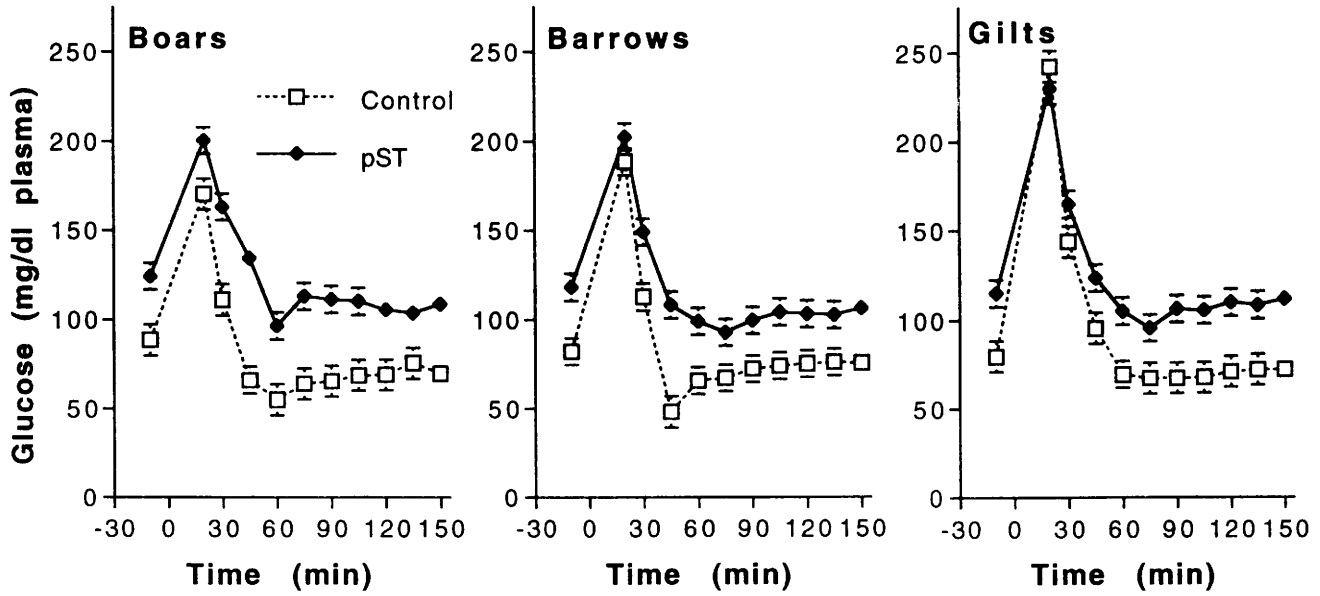

Figure 1. Temporal concentrations (mean ± SE) of glucose in fasted control and pST-treated boars, barrows and gilts during glucose tolerance test. Glucose concentrations were influenced by interactions of treatment and time ($P < 0.01$), and sex and time ($P < 0.05$).

in the "normal" fed state were collected at 15-min intervals for 8 hr beginning at 08:00 hr. At each sampling time, two samples were collected as described above. After collection of the 360-min sample at 1400 hr, porcine growth-hormone releasing factor (pGHRF, Peninsula Laboratories, Belmont CA, 5 μg/ml in 0.8% NaCl containing 0.01 *M* NaH_2PO_4, 0.01% ascorbic acid, and 0.1% hypophysectomized pig serum) was administered via the cannula, and the cannula was flushed with approximately 5 cannula volumes of saline. Dose of GHRF was 0.5 μg/kg body wt based on body weight obtained on Day 18. Hereafter, 0–6 hr of the sampling period is referred to as the period of normal secretion and the 6–8 hr period as post-GHRF.

Blood samples were immediately placed on ice after collection. Plasma for glucose measurement was harvested, within 60–90 min after collection, and glucose quantified by a colorimetric method on the day of collection (17). Plasma for measurement of pST, insulin, IGF-I, and IGF-II was harvested and frozen the afternoon of collection of the glucose tolerance test samples. However, plasma for pST, insulin, IGF-I, and IGF-II collected during the 8-hr sampling period was harvested and frozen the morning after sampling. Plasma concentrations of pST, insulin, IGF-I, and IGF-II were determined by radioimmunoassay (18, 19, 20, and 21, respectively). All samples were run in a single assay to avoid interassay variation. Intraassay measures of variation were below 10% for all RIAs.

Parameters of glucose clearance were calculated by methods of Tait and Burstein (22) assuming a one-component distribution pool. For the calculations, glu-

cose concentrations were transformed to logarithms and the data were truncated from the greatest sampling time until the data fit a linear line, to near 60 min. A linear regression was fitted to the data from each pig. The estimates of the glucose increase above the mean of the sample collection prior to glucose bolus administration, glucose distribution volume, glucose half-life ($t_{1/2}$) and glucose metabolic clearance rate (MCR) were calculated from the slope and Y intercept obtained from the regression equation. Metabolic clearance rate was expressed per animal and per unit metabolic body size (body weight in kg to the ¾ power).

The data were analyzed using the General Linear Models procedure of the Statistical Analysis System (23). Average daily gain was determined by linear regression. The model for analysis of growth performance and parameters of glucose clearance consisted of the effects of sex, pST dose (treatment), and resulting interactions. Initial weight was included as the covariate term in analysis of growth performance. Temporal changes in concentrations of plasma constituents were examined by split-plot analysis of variance (24). The model consisted of the effects of sex, pST dose, and resulting interactions tested by pig within sex by pST dose and effects of time and the interactions of the effects of sex and pST dose with time tested by the remaining variation. Data obtained during the 8-hr sampling period on Day 24 of treatment were analyzed using the split-plot model described above. The period of normal secretion and the post-GHRF period were analyzed separately. Least-squares means and standard errors were obtained for the significant effects and means were compared by protected t test.

Results

Administration of 4 mg pST·pig^{-1}/day by daily injection resulted in increased rate and efficiency of gain (Table I). There was a tendency for an interaction of sex and pST treatment on feed consumption ($P < 0.08$); the reduction in feed consumption induced by pST treatment was less in boars than in gilts or barrows.

Plasma glucose concentrations were increased ($P < 0.01$) with pST treatment in both the fasted (44%) and fed (64%) state (Table II, Fig. 1 and 2). Both calculated glucose distribution volume and half-life were approximately doubled while the MCR of glucose was reduced by 75% in the pST-treated pigs (Table II). Maximal insulin response to the loading dose of glucose was influenced by pST treatment ($P < 0.01$). In all groups, there was an increase ($P < 0.01$) in plasma insulin after administration of the glucose bolus (Fig. 3). This increase in control pigs was least in gilts, intermediate in barrows, and greatest in boars. The order of the response was reversed in pST-treated animals with a magnified insulin response to the glucose bolus in barrows and gilts. During the 6-hr period of blood sampling in the fed state insulin concentrations were greater ($P < 0.01$) in the pST-treated pigs, and no significant influence of sex was noted (Fig. 4).

Sex tended to affect circulating glucose concentrations in fasted ($P < 0.08$) and fed ($P < 0.05$) pigs (Table II, Fig. 1 and 2). Concentrations of glucose were greatest in boars, intermediate in barrows, and lowest in gilts, regardless of pST treatment. This ranking was preserved in the pST-treated pigs during the 6-hr sampling period. In control pigs during the 6-hr sampling

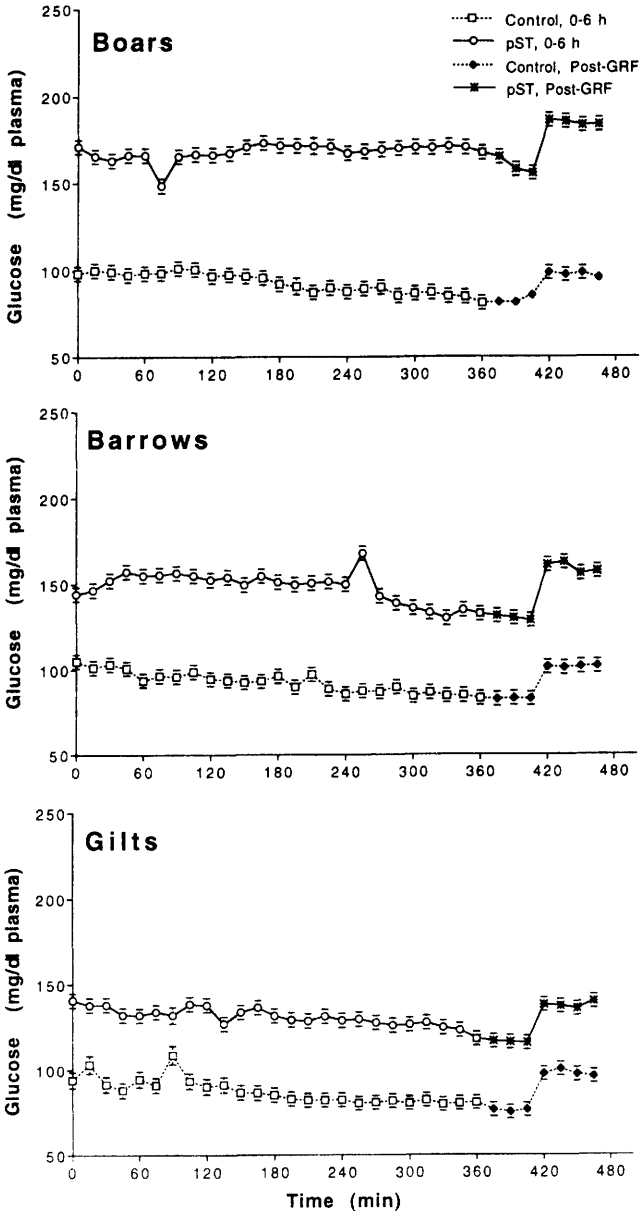

Figure 2. Temporal plasma concentrations (mean ± SE) of glucose in control and pST-treated pigs during 6-hr period of normal secretion and 2-hr period following administration of 0.5 μg GHRF/kg body wt. Temporal concentrations of glucose during the 6-hr period were influenced by interaction of treatment, sex, and time ($P < 0.01$). During the 2-hr period after administration of GHRF glucose concentrations were influenced by the interaction of treatment and time ($P < 0.02$).

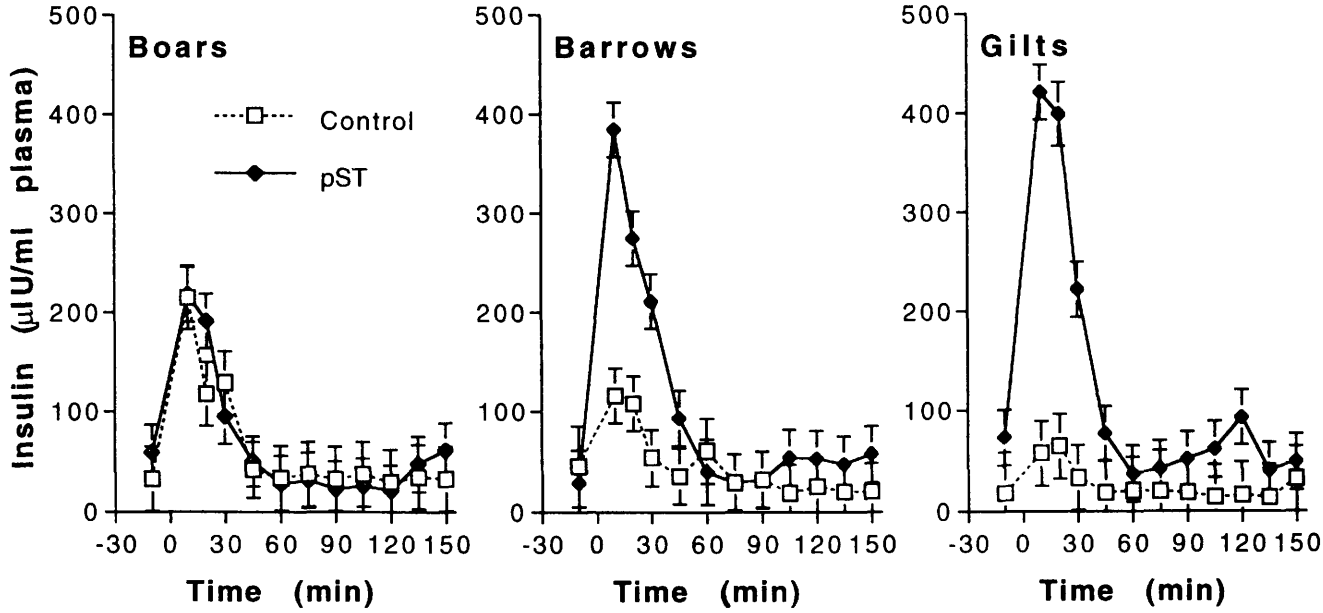

Figure 3. Temporal concentrations (mean ± SE) of insulin in fasted control and pST-treated boars, barrows, and gilts during glucose tolerance test. Insulin concentrations were influenced by the interaction of treatment, sex, and time ($P < 0.01$).

period, glucose concentrations were greatest in boars and barrows, both 93 mg/dl, and lower in gilts, 87 mg/dl.

Plasma concentrations of IGF-I were increased ($P < 0.01$) in the pST-treated pigs regardless of nutrient status and were not influenced by sex (Fig. 5 and 6). Administration of a loading dose of glucose had no effect on IGF-I concentrations. In contrast, IGF-II concentrations were not different between pST treatment groups in the fasted state (Fig. 5). During the 6-hr sampling period IGF-II concentrations tended to be reduced ($P < 0.08$) in pST-treated pigs in the fed state and were influenced ($P < 0.10$) by the interaction of sex and sampling time (Fig. 7). Mean concentrations across treatments in the boars were 190 ng/ml compared with 166 and 161 ng/ml in the barrows and gilts, respectively.

During the 6-hr sampling period, pST concentrations in the pST-treated pigs declined at a rate of 7.9 $ng \cdot ml^{-1}/hr$ (Fig. 8). Concentrations of pST across pST treatment groups were affected by sex ($P < 0.01$). Somatotropin concentrations in pST-treated pigs during the 6-hr sampling period were greatest in gilts and less

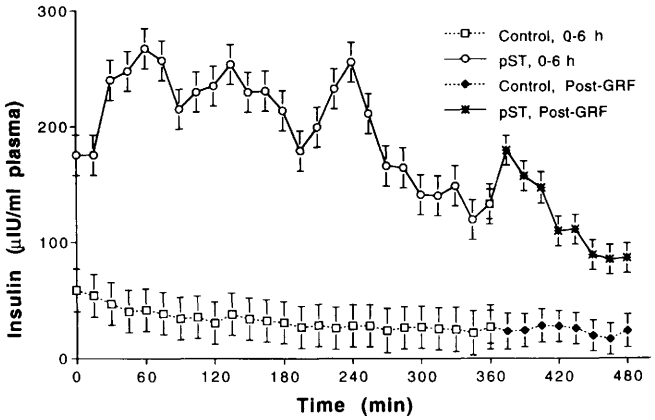

Figure 4. Plasma concentrations (mean ± SE) of insulin in control and pST-treated obese pigs during the 6-hr period of normal secretion and the 2-hr period following administration of 0.5 μg GHRF/kg body wt. Temporal concentrations of insulin during both periods were influenced by the interaction of treatment and time ($P < 0.01$).

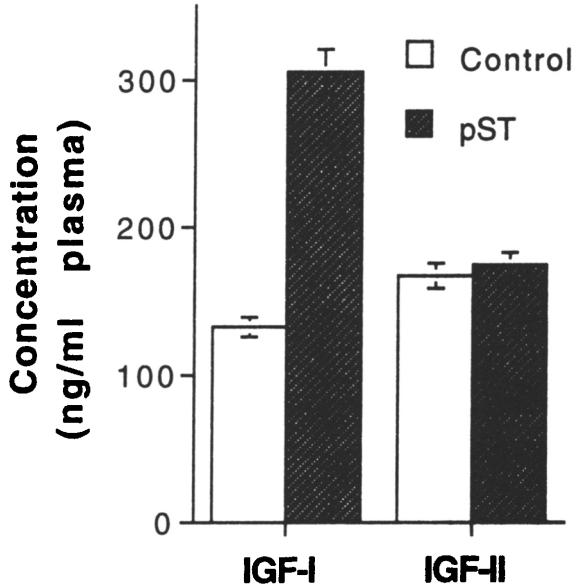

Figure 5. Concentrations (mean ± SE) of insulin-like growth factors, IGF-I and IGF-II, in fasted pigs during the glucose tolerance test. Concentrations of IGF-I were influenced only by treatment ($P < 0.01$). Treatment sex, time, and their interactions had no effect on IGF-II concentrations.

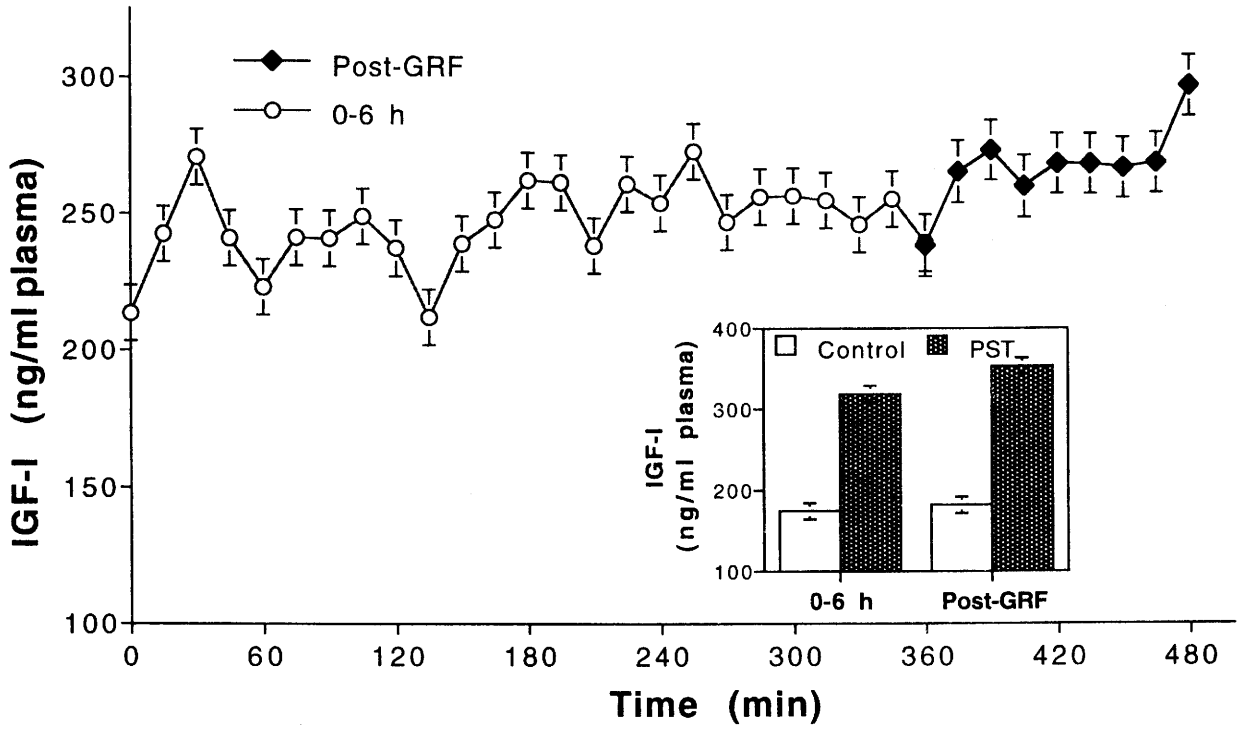

Figure 6. Plasma concentrations (mean ± SE) of IGF-I in control and pST-treated pigs during the 6-hr period of normal secretion and the 2-hr period following administration of 0.5 μg GHRF/kg body wt. Temporal concentrations of IGF-I during both periods were influenced by time ($P < 0.01$) and treatment (insert, $P < 0.01$). Temporal concentrations of IGF-I were not influenced ($P \leq 0.10$) by sex or interaction of sex with pST treatment or time.

in boars and barrows (51.2 ± 1.3, 43.5 ± 1.2, and 28.4 ± 1.2 ng/ml in gilts, boars, and barrows, respectively).

After blood sampling for 6-hr, on day 24, period of normal secretion, the pigs were administered 0.5 μg GHRF/kg body wt. In pigs chronically administered pST, there was no detectable pST response to the secretagogue (Fig. 8), whereas pST levels increased ($P < 0.05$) from 15 to 45 min after GHRF administration in the control pigs. Insulin was increased ($P < 0.01$) at 15 min after GHRF administration in the pST-treated pigs (Fig. 4), and glucose was increased ($P < 0.02$) about 1 hr after GHRF administration in both treatment groups (Fig. 2).

Discussion

The genetically obese pigs used in the present study were from a composite herd originating from Duroc and Yorkshire lines previously selected solely for high backfat thickness over multiple generations (14). The obese pigs, in the normal unchallenged state, are not hyperglycemic, hypertriglyceridemic, hypercholesterolemic, or hyperinsulinemic as compared with pigs of a contemporary line selected solely for low backfat thickness or crossbred pigs representing the current swine genotype (15). The magnitude of the hyperglycemia induced by exogenous pST is what distinguishes the genetically obese pigs from "normal" pigs. An objective of the present study was to investigate the pST induced hyperglycemia which occurs in all pigs administered pST, as well as other mammalian species administered ST, but is exaggerated in the genetically obese line of swine.

Plasma glucose concentrations were increased with pST treatment in both the fasted (44%) and fed (64%) state as observed previously in pigs of this genotype (5, 6). The increased half-life of glucose and reduced MCR suggest reduced uptake of glucose by the tissues (i.e., insulin resistance). It has been suggested the somatotropin-induced hyperglycemia is due to decreased glucose uptake by the tissues, particularly adipose tissue (8–10, 25, 26). This is supported by the observation that exogenous somatotropin treatment reduces the quantity of the glucose transporter, GLUT4, in membrane protein of porcine adipocytes (27). In addition, gluconeogenesis is increased by 23% in Yorkshire barrows treated with pST (11) and by 16% in hST-treated men (1). Thus, the increased circulating glucose, which may be partly due to decreased peripheral utilization, may also be the consequence of increased gluconeogenesis. These data and those of Wray-Cahen *et al.* (28) suggest that the half-life of plasma glucose is relatively short, 17–33 min. Thus, a major portion of the glucose that is present in elevated concentrations in these pigs, which were fasted for 26 hr, is the product of gluconeogenesis. Evidently these pST-treated pigs have a requirement for higher plasma concentrations of glucose, and gluconeogenic mechanisms are responding to that need.

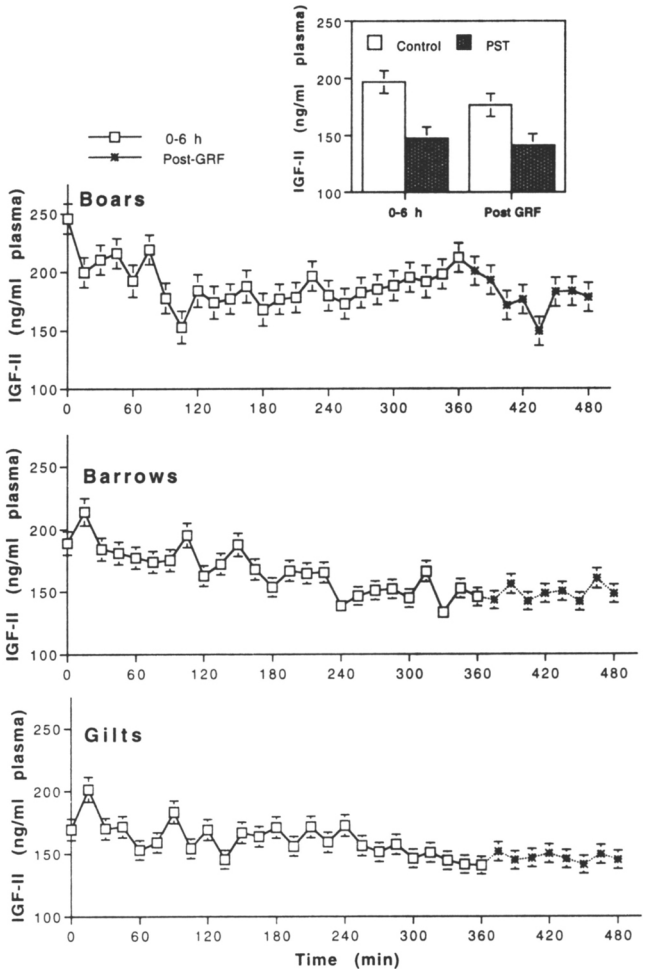

Figure 7. Plasma concentrations (mean ± SE) of IGF-II in control and pST-treated pigs during the 6-hr period of normal secretion and the 2-hr period following administration of 0.5 μg GHRF/kg body wt. Temporal concentrations of IGF-II during the 6-hr period were influenced by treatment (insert, $P < 0.08$) and an interaction of sex and time ($P < 0.10$). After GHRF administration IGF-II concentrations were influenced only by time ($P < 0.01$).

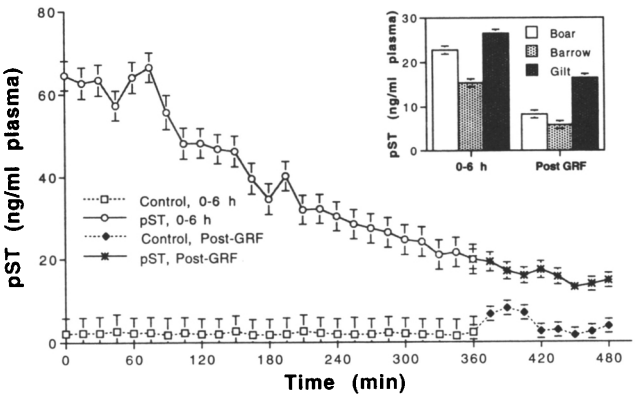

Figure 8. Temporal plasma concentrations (mean ± SE) of pST in control and pST-treated pigs during the 6-hr period of normal secretion and the 2-hr period following administration of 0.5 μg GHRF/kg body wt. Temporal concentrations of pST during the 6-hr period were influenced by interaction of treatment and time ($P < 0.05$). After administration of GHRF at 360 min pST concentrations were influenced by treatment ($P < 0.01$) and time ($P < 0.01$). During both periods pST concentrations were influenced by the main effect of sex ($P < 0.01$).

Following the loading dose of glucose, calculated glucose distribution volume and half-life were approximately doubled, while the MCR of glucose was reduced by 75% in the pST-treated pigs. Examination of the results of Wray-Cahen *et al.* (28) reveals similar effects of pST treatment on these parameters of glucose clearance. The increased half-life of glucose and reduced MCR suggest reduced uptake of glucose by the tissues. In all groups there was an increase in plasma insulin after administration of the glucose bolus. This increase in control pigs was least in gilts, intermediate in barrows, and greatest in boars. The order of the response was reversed in pST-treated animals with an exaggerated insulin response to the glucose bolus in barrows and gilts. This amplified insulin response in the presence of higher circulating glucose concentrations in pST-treated pigs is surprising, but is similar to the results presented by others (28, 29). One might expect that the elevated glucose concentrations would have depleted the readily available pool of pancreatic insulin. Apparently, the pancreatic β cells of the pST-treated animals are primed for greater response to glucose when presented the challenge. The boars, however, deviate from this scenario; peak insulin concentrations attained after the glucose bolus were similar in control and pST-treated boars. This lack of a pST effect on the insulin response could be due to the dose of glucose administered.

Somatotropin was administered approximately 75 min prior to the start of blood collection. Thus, the significant interaction of pST treatment and time during both blood sampling periods was expected. Surprisingly, sex influenced concentrations of pST across pST treatment groups. A sex effect on endogenous plasma ST concentrations in pigs, as well as other species, is well established (12, 30). Differences in circulating concentrations of exogenous pST among sexes suggests an effect on pST clearance. Somatotropin concentrations in pST-treated pigs during the 6-hr sampling period were greatest in gilts, less in boars, and least in barrows. These differences in pST concentration among the sexes could be due to differences in absorption from the injection site or the small differences in body weight at time of sampling. The most plausible explanation, however, may be differences among sexes in MCR of pST. We have previously suggested that the clearance of pST administered by a sustained release device is greater in barrows than gilts (6). Greater MCR of pST would result in lower concentrations of pST during the 7- to 8-hr period after administration. Arbona *et al.* (30) reported large, though nonsignificant, differences in MCR of pST in gilts and boars.

In pigs chronically administered pST, there was no detectable pST response to 0.5 μg GHRF/kg body weight. The failure of GHRF to induce a pST response in the pST-treated pigs may be due to exposure of the pituitary to a high level of somatostatin or to a lack of a readily releasable pool of pituitary pST. Both scenarios may be the consequence of high circulating concentrations of pST acting in a negative feedback manner, possibly through elevated IGF-I concentrations. Insulin was increased 15 min after GHRF administration in the pST-treated pigs, whereas glucose was increased about 1 hr after GHRF administration in both treatment groups. Hermansen *et al.* (31) reported human pancreatic (hp) GHRF-40 induced insulin and glucagon release from the perfused dog pancreas, and the insulin response was greater at higher glucose concentrations. Stimulation of insulin and glucagon release from the isolated rat pancreas by hpGHRF has also been reported (32). Elevated glucose concentrations following GHRF administration may be due to GHRF-induced glucagon release from the pancreas. Likewise, the elevated insulin concentrations may be a direct response to GHRF administration which is induced or enhanced with pST-treatment, possibly through the hyperglycemia. However, the glucose response 1 hr following GHRF administration may be the result of some centrally mediated response to anticipation of a meal rather than the consequence of GHRF administration. The pigs were accustomed to receiving their afternoon meal at 15:00 hr. On the day of blood sampling, that meal was not offered until after collection of the last sample at 16:00 hr.

Chronic administration of pST to swine of the genetically obese genotype results in reduced feed consumption and increased rate and efficiency of live weight gain. As a consequence of pST administration plasma concentrations of pST, IGF-I, insulin, and glucose are increased. The hyperglycemia is due to altered glucose regulation in pST-treated pigs; that is, decreased MCR of glucose, increased $t_{1/2}$ of glucose, elevated insulin concentrations, and altered insulin response to a glucose bolus (increased in barrows and gilts). Sex or gender influences several of the measures and responses to chronic pST treatment. Interestingly, plasma glucose concentrations are greater in boars than in barrows or gilts. Some of these sex differences are similar to the differences induced by pST treatment, and, therefore, responses to pST treatment may partially explain the sex differences in growth.

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