Exogenous growth hormone stimulates somatotropic axis function and growth in neonatal pigs

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Wester, Timothy J., Teresa A. Davis, Marta L. Fiorotto, and Douglas G. Burrin. Exogenous growth hormone stimulates somatotropic axis function and growth in neonatal pigs. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E29–E37, 1998.—We studied the effects of exogenous porcine growth hormone (pGH) administration on circulating insulin-like growth factor I (IGF-I) concentration, IGF-binding proteins (IGFBP), tissue growth, and protein synthesis in neonatal pigs. One-day-old pigs were given daily intramuscular injections of either pGH (1 mg/kg body wt) (n = 6) or saline (n = 5) for 7 days, after which time we measured in vivo protein synthesis using a bolus of [3H]-phenylalanine. Mean plasma for 7 days, after which time we measured in vivo protein synthesis rate in several visceral organs. Our results demonstrate that exogenous pGH increases circulating IGF-I and IGFBP-3 concentrations and visceral organ growth in neonatal pigs, suggesting that the somatotropic axis is functional in the neonate.

insulin-like growth factor I; protein synthesis; insulin; insulin-like growth factor-binding protein-3

POSTNATAL SOMATIC GROWTH is considered to be largely dependent on direct effects of growth hormone (GH) and its indirect anabolic effects, which are mediated via insulin-like growth factor I (IGF-I) (12). However, the prevailing dogma, that neonatal growth is GH independent, is based on limited evidence of normal birth weight in anencephalic infants and Laron-type dwarfs and also on relatively low hepatic GH binding and circulating IGF-I concentrations in neonates (8). These findings have raised doubts as to whether neonatal growth is GH responsive or if indeed the GH-IGF-I somatotropic axis is functional in the neonate.

However, recent studies suggest that GH responsiveness begins to develop before birth and is partially functional during the early neonatal period. Evidence from the rat indicates an upregulation of GH-receptor mRNA with increasing fetal age to 10% of adult levels at birth with concurrent activation of GH-responsive mRNAs (2, 20). Furthermore, other recent studies have shown that somatic growth in neonatal rats, reduced 50% after hypophysectomy, can be restored with GH replacement therapy (22), and spontaneous dwarf rats, which exhibit isolated GH deficiency, are born with significantly reduced birth weight relative to control rats (28). In addition, Lumpkin et al. (32) demonstrated that ablation of GH secretion by a GH-releasing factor receptor antagonist resulted in cessation of somatic growth in weanling rats despite maintenance of normal nutrient intake.

Numerous studies have shown that exogenous administration of GH to adult pigs significantly increases weight gain and the efficiency of dietary nutrient utilization for protein deposition (15, 16, 17, 29). GH administration to adult pigs is also associated with increases in circulating glucose and insulin concentrations, suggesting insulin resistance of glucose metabolism (14, 23, 43). However, the few studies in neonatal pigs have demonstrated a lack of growth response to exogenous GH (1, 25). This apparent lack of effect may be attributable to the relatively low plasma and hepatic GH binding capacity of the neonatal pig (3, 37), which would reduce both the responsiveness and sensitivity to exogenous GH compared with adult pigs. The dose of GH administered in these studies was similar to that used previously in adult pigs (25). The dose used in adult pigs, however, may have been insufficient to elicit a biological response in the neonate if the sensitivity of the tissues to GH is reduced, and/or if GH is cleared more rapidly from the circulation due to lower plasma binding capacity.

The objective of this study was to determine whether neonatal pigs are responsive to exogenous porcine GH (pGH). To maximize the likelihood of inducing a response, we administered pGH at a dose that was higher than is typically used for adult pigs, and which was given in three daily doses rather than as a single injection. We have determined the effect of exogenous pGH on the circulating IGF-I concentration to test whether the somatotropic axis is functional in neonatal pigs. In addition, we have characterized tissue growth and metabolism to establish whether, in the neonatal pig, pGH can induce a biological response, either directly or indirectly via IGF-I.

MATERIALS AND METHODS

Animals and design. Two litters of conventional crossbred newborn pigs (Texas A&M University, College Station, TX) were obtained immediately after birth and weighted. Before the start of the experiment and after each pig had been 12 h with the sow, a 20-gauge Silastic catheter was surgically inserted into the jugular vein of each pig, with the animals under general isoflurane anesthesia. Pigs were allowed to recover for at least 1 h before the start of the experiment. Pigs were housed two to three per cage at an ambient temperature of 20°C. Pigs were assigned randomly to receive either recombinant pGH (Monsanto, St. Louis, MO) at a daily dose of 1 mg/kg body weight (n = 6) or saline (n = 5) in three equal, intramuscular injections daily. To eliminate any possible...
and electrophoresed at 110 V overnight at 4°C through a 3% bromophenol blue, pH 6.8], placed in boiling water for 5 min, buffer [62.5 mM tris(hydroxymethyl)aminomethane (Tris), 23 of plasma from each animal were diluted 1:10 in sample modified Western ligand blot procedure (26). Equal volumes of IGF-binding proteins (IGFBP) was performed using a solution. The activity of the tracer buffer (TBS containing 1 ml/l NaCl, pH 7.4) for 2 h. Blots were then returned to the first buffer for 10

Blood sampling protocol. Venous blood (2 ml) was sampled daily for analysis of plasma IGF-I and urea nitrogen (PUN) concentrations. After 7 days of treatment, serial blood samples were taken from all pigs to determine the plasma GH secretory profile and the glucose and insulin response to feeding. The morning of day 7 of treatment, after an overnight fast, blood samples (1 ml) were obtained. Immediately thereafter, the pigs received a formula feeding (40 ml/kg body wt) and either a saline or pGH (333 µg/kg body wt) injection, and then blood sampling was continued every 20 min for 4 h. All samples were taken with the use of heparinized syringes, and plasma was harvested and stored at −70°C until analysis.

Plasma IGF-I, insulin, GH, PUN, and glucose. Plasma IGF-I concentration was measured by radioimmunoassay after acidification and chromatography to remove binding proteins (7). Plasma insulin and glucose concentrations were measured in the first six serial samples. Plasma insulin was measured by radioimmunoassay (Linco Research, St. Louis, MO). The human-specific antibody used in this assay exhibited 100% cross-reactivity with porcine insulin. Intra- and interassay coefficients of variation were 2.8 and 2.9%, respectively. All samples were measured in one assay, and the intra-assay coefficient of variation was 6.9%. Plasma GH concentration was measured by double-antibody homologous radioimmunoassay (42). All samples were measured in one assay, and the intra-assay coefficient of variation was 4.4%. The secretory profile of GH was analyzed using the Pulsar peak-fitting program to estimate the mean GH concentration. Plasma glucose was measured by an automated glucose oxidase procedure (Yellow Springs Instruments, Yellow Springs, OH). PUN concentration was measured using an endpoint enzymatic assay (Roche, Somerville, NJ).

Ligand blot analysis of plasma IGF-binding proteins. Analysis of IGF-binding proteins (IGFBP) was performed using a modified Western ligand blot procedure (26). Equal volumes of plasma from each animal were diluted 1:10 in sample buffer [62.5 mM tris(hydroxymethyl)aminomethane (Tris), 23 g/l sodium dodecyl sulfate, 100 mM glycerol, and 0.5 g/l bromophenol blue, pH 6.8], placed in boiling water for 5 min, and electrophoresed at 110 V overnight at 4°C through a 3% stacking on a 12% resolving gel. Approximately 1-3 µl of plasma were run in each lane. Proteins were electrotransferred to a nitrocellulose membrane at 200 mA for 3 h at room temperature. Before ligand binding, blots were incubated for 30 min in Tris-buffered saline (TBS; 10 mM Tris, 150 mM NaCl, pH 7.4) containing 30 µl Triton X-100 followed by blocking buffer (TBS containing 70 µl nonfat dry milk, pH 7.4) for 2 h. Blots were then returned to the first buffer for 10 min. Incubations were performed overnight with gentle shaking. The activity of the tracer buffer (TBS containing 1 ml/l Tween-20, 20 g/l nonfat dry milk, and radioligand, pH 7.4) was 130 kBq[125I]-labeled IGF-I per blot in 50 ml of solution. Blots were washed at room temperature twice for 15 min in a buffer containing TBS containing 1 ml/l Tween-20, pH 7.4, and three times for 15 min in TBS. Blots were dried at room temperature and then exposed to X-ray film in the presence of intensifying screens at −70°C for 7 days. The band intensities on the autoradiographs were quantified using laser densitometry (Pharmacia LKB Biotechnology, Piscataway, NJ). Relative molecular weights of IGFBPs were estimated by comparison to Coomassie blue-stained protein standards run under identical conditions.

Immuno blotting and immunoradiometric analysis of plasma IGFBP. For Western blotting, plasma samples were diluted 1:4 in sample buffer (see above), placed in boiling water for 5 min, and electrophoresed at 200 V for 2 h at 4°C through a 3% stacking on a 12% resolving gel. Approximately 2.5 µl of plasma were loaded in each lane. Proteins were electrotransferred from the gel to a nitrocellulose membrane at 100 V for 3 h at 4°C. Immunoblotting was performed using the following dilutions of antibodies: 1:2000 dilution of antibody IGFBP-2 polyclonal rabbit antiserum (Upstate Biotechnology, Lake Placid, NY) and 1:1,000 dilution of anti-human IGFBP-3 polyclonal rabbit antiserum (Diagnostic Systems Laboratories, Webster, TX). For direct comparison of proteins identified by ligand blotting and immunoblotting, sections of Western blots were cut and developed using both ligand blotting (see above) and immobil blotting procedures. Immunoblotting was performed using the following dilutions of antibodies: 1:100 dilution of antibody IGFBP-3 polyclonal rabbit antiserum (Diagnostic Systems Laboratories, Webster, NY) and 1:1,000 dilution of antihuman bovine IGFBP-2 polyclonal rabbit antiserum (Upstate Biotechnology, Lake Placid, NY). The human-specific antibody used in this assay exhibited 100% cross-reactivity with porcine insulin. Intra- and interassay coefficients of variation were 2.8 and 2.9%, respectively. All samples were measured in one assay, and the intra-assay coefficient of variation was 6.9%. Plasma GH concentration was measured by double-antibody homologous radioimmunoassay (42). All samples were measured in one assay, and the intra-assay coefficient of variation was 4.4%. The secretory profile of GH was analyzed using the Pulsar peak-fitting program to estimate the mean GH concentration. Plasma glucose was measured by an automated glucose oxidase procedure (Yellow Springs Instruments, Yellow Springs, OH). PUN concentration was measured using an endpoint enzymatic assay (Roche, Somerville, NJ).

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Tissue samples (100–200 mg) were homogenized in water, and aliquots were removed for analysis of protein and DNA using biocinchoninic acid (41) and bis-benzimide (30), respectively. The specific radioactivity of $[3H]$phenylalanine was determined in whole blood samples and in the tissue samples as described previously (3). The tissue homogenate was acidified with 2 M perchloric acid (PCA) and processed as described previously (6). In brief, homogenate supernatants containing the tissue free amino acid pool were separated from PCA-insoluble precipitates and neutralized. PCA-insoluble precipitates were washed and solubilized. The solution was reacidified, and the acid-soluble fraction was assayed for RNA (35). The protein-containing pellet was washed and hydrolyzed for 24 h in 6 M HCl. The protein hydrolysate, homogenate supernatant, and blood supernatant were vacuum-dried and resuspended in water for determination of phenylalanine specific activity. Phenylalanine was separated from other amino acids using anion exchange chromatography. Radioactivity associated with the collected phenylalanine fraction was measured using liquid scintillation counting.

Calculations. Protein synthesis was calculated as a fractional rate (FSR, %/day) from the equation described by Garlick et al. (21)

$$FSR = \left( \frac{S_b}{S_a} \right) \times \left( \frac{1440}{t} \right) \times 100$$

where $S_a$ is the specific activity of the PCA-insoluble or protein-bound phenylalanine pool (Bq/µmol), $S_b$ is the specific activity of the PCA-soluble or tissue free phenylalanine pool (Bq/µmol), and $t$ is time of labeling in minutes. The value used for $S_a$ was corrected to represent the average tissue free phenylalanine specific activity at the midpoint ($t$) of the 30-min labeling period. The corrected $S_a$ for each pig was calculated by adding individual tissue $S_a$ values (Bq/µmol) after time ($t$) and the rate of change in blood $S_a$ (Bq·µmol$^{-1}·$min$^{-1}$) estimated from the regression of 5-, 15-, and 30-min blood samples of all pigs within a treatment group as described previously (5).

Corrected tissue $S_a = \text{tissue } S_{a0} + (\text{blood } S_a \cdot t)$

Absolute synthesis rate (ASR, g protein/day) was calculated as the fractional rate times the tissue protein content. Protein synthetic efficiency (mg protein·day$^{-1}·$mg RNA$^{-1}$) was calculated as total daily protein synthesized per total RNA. Protein synthetic capacity (g RNA/mg protein) was estimated by the RNA to protein ratio.

Statistical analysis. Data consisting of single observations in time, e.g., tissue weights, substrate dissociation constant, and plasma GH profile, were analyzed by one-way analysis of variance (ANOVA) with treatment as the main effect. Observations taken across time, e.g., daily plasma hormone and metabolite concentrations, were analyzed by repeated-measures ANOVA, with treatment and sampling time as main effects. Differences with $P < 0.05$ were considered significant. Results are presented as means with pooled SD from the one-way ANOVA or as means ± SE.

RESULTS

Plasma GH, IGF-I, and IGFBP. Measurements taken after 7 days of treatment indicated that administration of exogenous pGH on average resulted in a 22-fold increase in plasma GH concentration above the mean GH level of controls (Fig. 1). Within 1 h of dosing, the exogenous pGH completely obliterated any endogenous secretory pulses and resulted in mean plasma GH levels nearly 40 times those of controls (14 vs. 539 ng/ml, control and pGH-treated, respectively; $P < 0.01$), which then decreased to 11 times that of controls (14 vs. 151 ng/ml, control and pGH-treated, respectively; $P < 0.01$) by the end of the sampling period, 4 h after dosing.

After 1 day of pGH administration, plasma IGF-I was elevated above controls (32.1 vs. 54.2 ng/ml, control and pGH-treated, respectively; $P = 0.09$) and continued to increase until it reached a plateau value ~300% of that of controls on day 4 of treatment (Fig. 2). In ligand blots of plasma samples collected after 7 days of treatment, we identified five bands of IGFBP binding that corresponded to apparent molecular weights of 43, 39, 33, 29, and 24 kDa (Fig. 3). These bands were putatively identified by comparing them with bands in published reports that used immunological methods (31, 34, 40) as differentially glycosolated forms of IGFBP-3 for the 43- and 39-kDa bands, IGFBP-2 for the 34-kDa band, IGFBP-1 for the 29-kDa band, and IGFBP-4 for the 24-kDa band. Commensurate with these previous reports, we found, on the basis of immunoblotting, that the anti-human IGFBP-3 antiserum recognized only the 43- and 39-kDa proteins and the anti-human IGFBP-2 antiserum recognized only a 34-kDa protein (Fig. 3). Although we did not verify immunologically the 29- and 24-kDa bands observed by ligand blotting, we believe these to be the same proteins previously identified as IGFBP-1 in neonatal pig serum (34) and IGFBP-4 (40), respectively. Moreover, because the 29- and 24-
kDa bands were not detected by immunoblotting with IGFBP-2 and -3 antibodies, it is unlikely that they are proteolytic products of either IGFBP-2 or IGFBP-3 degradation. On the basis of ligand blotting, when expressed as a percentage of the total plasma IGFBP abundance, the proportions of IGFBP-1 and IGFBP-2 were lower (\( P<0.05 \)) and those of IGFBP-3 and IGFBP-4 were higher (\( P<0.05 \)) in pGH-treated than in control pigs (Fig. 4). The abundance of plasma IGFBP-3 measured by immunoblotting was approximately three-fold higher in pGH-treated than in control pigs; however, there was no difference in the abundance of IGFBP-2 (Fig. 5). When measured by the immunoradiometric assay, IGFBP-3 was nearly twofold higher in pGH-treated than in control pigs (88.7 ± 4.3 vs. 149.2 ± 5.5 ng/ml, control and pGH-treated, respectively; \( P<0.01 \)).

PUN, glucose, and insulin. During the 7-day treatment period, PUN concentrations were not statistically different (\( P>0.05 \)) between control and pGH-treated pigs (Fig. 6). However, with the exception of day 4, PUN tended to be lower (ranging from 15 to 48%) in pGH-treated than in control pigs. To determine whether 7 days of pGH treatment resulted in insulin resistance, plasma insulin and glucose concentrations were measured in response to feeding after an overnight fast. Although the plasma insulin response in the first 60 min after feeding appeared to be blunted in the pGH-treated compared with control pigs, there was no difference in the area under the plasma insulin curve between treatments (4,423 ± 612 vs. 3,646 ± 378 \( \mu \text{U} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}, \) control and pGH treated, respectively) (Fig. 7). The plasma glucose concentration after feeding was greater at all time points in pGH treated pigs compared with controls. Thus the area under the plasma glucose curve in response to feeding was greater in pGH-treated than control pigs (843 ± 50 vs. 1,084 ± 63 mmol·l\(^{-1}·\text{min}^{-1}, \) control and pGH-treated, respectively; \( P<0.05 \)) (Fig. 7).

Body weight gain, organ growth, and protein synthesis. Body weights of pGH-treated pigs were 10% greater than those of control pigs after 7 days of treatment.
During the 7 days of treatment, the rate of body weight gain was faster (+15%) and weight gain per unit of food intake, commonly referred to as food conversion efficiency, was greater (+16%) in pGH-treated pigs than control pigs (P < 0.05, Table 1). Among the various organs measured, liver (+24%), kidney (+16%), jejunum (+22%), and heart (+18%) weights were significantly (P < 0.05) greater after 7 days of pGH treatment. When organ weights were normalized to body weight (g/kg body wt), the liver (45.2 vs. 36.5, SD = 2.7, P < 0.01) and kidney (8.81 vs. 7.62, SD = 0.54, P < 0.01) were still greater in pGH-treated than in control pigs, respectively.

The tissue protein contents of the kidney (+41%), stomach (+36%), and jejunum (+25%) were significantly greater in pGH-treated than control pigs (Table 2); the protein content of the liver and heart also tended to be greater (P < 0.10) in pGH-treated than control pigs. There were no differences between treatments for tissue concentrations of protein, RNA, and DNA (data not shown).

The FSR values in all of the tissues measured were similar (P > 0.05) in control and pGH-treated groups (Table 2). However, the ASR values for liver (+39%), kidney (+49%), stomach (+41%), jejunum (+47%), and heart (+43%) were greater in pGH-treated pigs than in controls (P < 0.05). The ASR of the soleus muscle (+18%) and lung (+21%) tended to be greater in pGH-treated vs. control pigs (P < 0.10). In addition,
protein synthetic capacity was increased (+14%, P < 0.05) in liver, and the protein synthetic efficiency was increased (+31%, P < 0.05) in semitendinosus of pGH-treated pigs compared with controls (data not shown).

DISCUSSION

It is widely believed that neonates are unresponsive to GH and that neonatal growth, therefore, is relatively GH independent. However, few studies have examined the effects of exogenous GH on growth or the function of the somatotropic axis in neonates. Our current study has demonstrated that pGH administered to neonatal pigs results in increased plasma concentrations of IGF-I, IGFBP-3, and glucose and elevated body weight gain and visceral organ protein synthesis. These changes in neonatal pigs are characteristic of the metabolic and anabolic response to GH treatment, although the magnitude of the responses is considerably lower than observed previously in more mature pigs. Nevertheless, the results indicate that the somatotropic axis in neonatal pig is, indeed, responsive to exogenous pGH.

Endocrine effects of GH. Our results demonstrate that pGH administration to neonatal pigs produced the characteristic stimulation of the somatotropic axis as evidenced by the marked increase in the circulating IGF-I concentration compared with control pigs. The temporal increase in circulating IGF-I noted in the initial 4 days of pGH treatment may reflect a gradual increase in GH responsiveness and is supported by evidence of upregulation of both hepatic GH-binding and GH-receptor mRNA abundance in response to chronic pGH treatment in pigs (1, 4, 9). Previous studies of GH administration to neonatal pigs have reported variable effects on circulating IGF-I concentrations, due to the differences in the GH dose and frequency of administration used (1 vs. 3 times per day) compared with our study (1, 25, 33). However, the two- to threefold increase in circulating IGF-I concentration that we observed in pGH-treated neonatal pigs is consistent with values reported recently (33) in neonatal pigs at a slightly lower dose (~0.5 mg/d) than we used and in mature pigs, albeit at much lower doses (11, 16, 29, 43).

At least two possible mechanisms are responsible for the increase in circulating IGF-I in pGH-treated neonatal pigs. The first is increased endogenous IGF-I production and several tissues, including liver, adipose tissue, and certain skeletal muscles, have been shown to be GH responsive, as measured by increased IGF-I mRNA expression (4, 11). Therefore, the increased circulating IGF-I concentration in pGH-treated neonatal pigs in our study was likely a result of increased tissue expression, and, indeed, recent evidence indicates that administration of pGH increases hepatic IGF-I expression in neonatal pigs (33). Our results suggest that a second mechanism responsible for the increased circulating IGF-I was an increase in plasma IGFBP-3 concentration, which may have prolonged the half-life of IGF-I. In adults, IGFBP-3 is the most abundant IGFBP and has the greatest affinity for both IGF-I and -II (27). In neonates, however, the plasma levels of IGFBP-2 are higher and those of IGFBP-3 are lower compared with those of adults (13). On the basis of measurements of ligand binding, immunoblotting, and immunoradiometric assay, our results indicate that pGH treatment increased both the absolute concentration and relative abundance of plasma IGFBP-3. The changes in the abundance of plasma IGFBP-3 induced by pGH treatment in our study were similar to those observed in 14-wk-old pigs (10). Thus, given that most of the circulating IGF-I is bound to IGFBP-3, which does not leave the vascular compartment, we would postulate that the increased circulating IGF-I in the pGH-treated pigs was partially a result of a longer half-life. The increased plasma IGFBP-3 was likely a result of the increase in circulating IGF-I concentrations in response to pGH treatment (27, 46). Thus, on the basis of the changes in both circulating IGF-I and IGFBP concentrations, our results demonstrate that the somatotropic axis in neonatal pigs, even as early as 2 days of age, is responsive but considerably less sensitive to pGH treatment than that of adult pigs, given the higher dose of exogenous pGH required to attain the similar changes.

Metabolic effects of GH. One of the classic metabolic effects of GH treatment is the diabetogenic effect that is manifested as insulin resistance (36). Insulin resistance in pGH-treated adult pigs is characterized by increased circulating concentrations of both glucose and insulin; the hyperglycemia results from both increased hepatic production and decreased peripheral glucose clearance (14, 23). Our results, based on the meal-tolerance test after 7 days of pGH treatment, indicated that these pigs were becoming insulin resistant. The presence of hyperglycemia, despite equal circulating insulin concentrations, in pGH-treated pigs is consistent with either increased hepatic production or decreased glucose clearance, indicating insulin resistance of glucose metabolism. The diabetogenic effect of pGH on glucose metabolism, which we observed in the neonate, was, however, somewhat blunted compared with the responses reported in more mature pigs (23, 44). This more blunted hyperglycemic effect suggests that the neonatal pig may be less sensitive to pGH compared with the adult pig. Alternatively, our previous observations that the insulin responsiveness of glucose disposal is elevated in early neonatal compared with late neonatal or adult pigs (43, 44) may perhaps explain why this diabetogenic effect of pGH treatment on glucose metabolism was somewhat blunted compared with the adult pig. It has been shown that the diabetogenic effect of pGH on glucose metabolism is mediated particularly through decreased glucose utilization by adipose tissue (14, 22). Therefore, neonatal pigs may be less sensitive to the diabetogenic effects of pGH on glucose metabolism because they have a considerably lower body fat content than adult pigs (39).

Another characteristic metabolic effect of GH treatment is reduced PUN concentrations, an effect that has been shown to be dependent on dose and frequency of administration (16, 17, 45). Recent studies in neonatal
pigs given much lower doses than in the current study suggest that the reduction in PUN after pGH treatment does not become responsive until ~3–4 wk of age, concurrent with the increase in hepatic GH binding (25). Consistent with this previous report, we found no significant PUN response, which may have been because the neonatal pig is less sensitive to pGH compared with the adult pig, as well as an inherently large between-animal variability. Moreover, in our study, pigs were fed dietary protein in excess of their requirement to ensure that any growth-promoting effects of pGH could be achieved. This may have masked any subtle changes in the efficiency of protein utilization, as reflected by PUN.

Body weight gain, tissue growth, and protein synthesis. Two of the fundamental anabolic effects of GH treatment in pigs are increased body weight gain and food conversion efficiency that result from the increased deposition of lean and reduction of adipose tissue (15, 16). We observed pGH responses in both body weight gain and food conversion efficiency in neonatal pigs that were similar to those reported for older pigs given exogenous GH (15, 17, 38). It should be noted that the increases in organ protein content in response to pGH treatment were not associated with a decrease in the protein concentration (i.e., mg/g tissue) in any tissue measured, indicating that the increase in tissue weight was not due to changes in tissue hydration but to a net increase in protein deposition. The combined protein content of all the tissues or organs measured was increased ~17% by pGH treatment, similar to the increase in body weight gain, suggesting that the growth response was allometric. However, the sum of all the tissues measured, mostly internal organs, represents a relatively small proportion (13–14%) of body weight. Thus an unanswered question is whether the growth response occurred in the proportionally larger mass of carcass tissues composed of skeletal muscle, bone, adipose, and skin. It is unlikely that changes in adipose tissue mass contributed to the differences in body weight gain in response to pGH treatment, since the body fat content of the neonatal pig is relatively low (1–2%) (39). Although we did not measure body composition, we found only modest increases in the protein content of both soleus (+10%) and semitendinosus (+3%) muscles, indicating that skeletal muscle protein deposition was minimally responsive to pGH treatment in neonatal pigs.

In the present study, we did not observe any statistically significant increase in the FSR for any tissue measured. However, we observed that the ASR of protein was significantly greater in several tissues, which reflected the higher tissue protein content in pGH-treated than control pigs. The tissues in which pGH treatment produced the largest stimulation of protein ASR were the kidney, jejunum, stomach, and liver. Although several reports have noted enhanced skeletal muscle protein synthesis in response to administration of either GH or IGF-I, we observed only minimal effects (18, 19, 38). The fact that we did not detect any significant increases in FSR suggests that the increased protein content observed in several tissues from pGH-treated pigs resulted from either a decrease in the fractional rate of protein degradation or that an increase in the FSR occurred earlier in the treatment period. It was notable, however, that, despite a threefold increase in circulating IGF-I concentration, protein synthesis and weight gain were only modestly increased compared with the responses reported in more mature animals (15, 17, 18, 38). Thus, whereas the somatotropic axis is functional in the neonatal pig, an increase in the circulating IGF-I concentration above normal resulted in only a modest stimulation of growth. This relatively modest response to increased circulating IGF-I may be a consequence of the existing high rates of growth and anabolism in the neonatal pig that cannot be increased further.

Perspectives. The results indicate that the somatotropic axis in neonatal pigs is functional and responsive to exogenous pGH. Although we found that the proportional increases in circulating IGF-I and IGFBP-3 concentrations in response to exogenous pGH were similar to those observed in previous studies with adult pigs, the pGH dose we used was severalfold greater. This suggests that the somatotropic axis in neonatal pigs is less sensitive to exogenous pGH than in adult pigs. Despite the pharmacological dose of pGH and the nearly threefold increase in circulating IGF-I, the metabolic and anabolic growth responses we observed were relatively modest, suggesting that neonatal pigs are less sensitive not only to exogenous pGH but also to circulating IGF-I, compared with adult pigs.

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