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Original article

Effect of a growth hormone infusion on plasma insulin-like growth factor-I in Meishan and Large White pigs

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Summary — Plasma growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels were determined in Large White (LW) and Meishan (MS) female pigs at 80 and 185 days of age before and after an infusion of porcine GH. Plasma GH concentration declined with age and was similar in both breeds. Plasma IGF-I concentration did not differ between MS and LW pigs at 80 days of age. It increased with age in LW pigs whereas it remained almost unchanged in MS pigs. GH infusion led to an increase in plasma GH concentration and elicited a rapid and persistent rise in plasma IGF-I levels in both breeds. IGF-I response to GH was lower in LW than in MS pigs at 80 days, whereas the reverse was observed at 185 days of age. It increased with age in LW while it declined in MS pigs. The present results suggest the development of a GH resistance in MS pigs. This is likely associated with sexual maturity. Whether such GH resistance would also be observed in postpubertal LW female pigs remains to be investigated.

pig / breed / GH / IGF-I

Résumé — Effet d'une perfusion d'hormone de croissance (GH) sur l'IGF-I *(insulin-like growth factor-I)* dans le plasma de porcs Large White et Meishan. *Les niveaux de GH et d'IGF-I ont été déterminés à 80 et à 185 jours d'âge dans le plasma de porcs femelles de race Large White (LW) et Meishan (MS). La concentration plasmatique de GH diminue avec l'âge et elle est similaire chez les porcs LW et MS. La concentration plasmatique d'IGF-I ne diffère pas entre les porcs LW et MS à 80 jours d'âge. En revanche, alors que cette concentration augmente avec l'âge chez les porcs LW, elle reste inchangée chez les porcs MS. La perfusion de GH conduit à une augmentation de la concentration plasmatique de GH et à une augmentation rapide et persistante des niveaux plasmatiques d'IGF-I dans les deux races. Néanmoins, à 80 jours d'âge, l'augmentation de l'IGF-I est plus faible chez les porcs LW que chez les porcs MS et, à 185 jours d'âge, l'inverse est observé. Ces résultats suggèrent le développement avec l'âge d'un état de résistance à la GH chez les porcs MS, qui est probablement en liaison avec la maturation sexuelle. Il reste à déterminer si une telle résistance à la GH serait également observable chez les porcs femelles de race LW après la puberté.*

porc / race / GH / IGF-I

INTRODUCTION

Growth hormone (GH) plays a major role in growth regulation. In pigs, numerous studies have shown that GH administration dramatically alters growth performance (eg, Chung et al, 1985). The effects of GH are thought to be mediated at least in part by insulin-like growth factor-I (IGF-I), which circulates in the blood, bound to specific binding proteins (Rechler and Brown, 1992). In pigs, plasma levels of IGF-I increase after the administration of GH (Etherton et al, 1987; Sillence and Etherton, 1987; Owens et al, 1990).

Meishan (MS) pigs grow more slowly than conventional pigs and have a greater adipose tissue development and reduced muscle accretion (Bonneau et al, 1990; White et al, 1995). In addition, puberty occurs earlier in MS than in Large White (LW) pigs (Camous et al, 1985; Prunier et al, 1993). However, the mechanisms underlying these differences are unknown. The slower growth of MS pigs may be due to an alteration of the GH/IGF-I axis. A deficiency in GH secretion seems unlikely, since the plasma GH concentrations are similar in MS and LW pigs between 10 and 140 days of age (Louveau et al, 1991). Alternatively, MS pigs may be less responsive to GH than LW pigs. One way of investigating the responsiveness to GH is to monitor plasma IGF-I levels following GH administration.

The aim of the present study was to evaluate the changes in plasma IGF-I levels with age and in response to GH in both MS and LW pigs. The same animals were studied at 80 and then at 185 days of age in order to compare LW and MS pigs at a similar stage of pubertal development (80-day-old MS vs 185-day-old LW).

MATERIALS AND METHODS

Animals and experimental design

IGF-I responses to GH were measured at two ages in six MS and six LW female pigs, chosen from six litters per breed. The same animals were studied at both ages. MS animals at 80 and 185 days of age weighed 18.7 ± 1.2 kg and 72.9 ± 2.5 kg, respectively. LW animals at 80 and 185 days of age weighed 29.6 ± 1.4 kg and 107.5 ± 1.2 kg, respectively. All the animals were fed ad libitum a diet formulated to contain 12.9 MJ of digestible energy per kg and 17.3% protein. They were placed in individual pens and had free access to water. Two catheters were inserted into an external jugular vein under general anesthesia (2 ml/min O_2-halothane 92:8 v/v) 3 days before each measurement period (80 and 185 days of age). The catheters were kept patent with heparinized saline.

On the first day of each period, blood samples were collected through one of the catheters at 20 min intervals for 8 h, starting at 0900 hours. On the second day, recombinant porcine GH (Pitman-Moore, Inc, Lot BV-90-A-0001, Terre-Haute, IN, USA) was infused in sterile saline through the second catheter from 1000 to 1500 hours. The administered doses were 9.4 ± 0.2 μg/kg per hour at 80 days and 7.2 ± 0.2 μg/kg per hour at 185 days.

Blood sampling began 1 h prior to the GH infusion and was continued for 72 h. From 0900 to 1700 hours, samples were collected at 20 min intervals and then at 7, 9, 11, 13, 15, 19, 23, 29, 35, 47 and 71 h after the onset of the GH infusion.

Blood samples were collected in heparinized syringes (20 U/ml blood), cooled on ice and centrifuged. Plasma samples were stored at –20 °C until analysis.

Determination of plasma GH and IGF-I concentrations

Double antibody radioimmunoassay procedures were used to determine the plasma GH and IGF-I concentrations. Plasma GH concentration was measured in all samples using pGH (USDA-B1,

AFP-5100) as a standard and pGH provided by Dr AF Parlow for iodination, according to a previously described procedure (Bonneau, 1993). The samples collected in order to determine plasma GH profile (day 1) and those collected during and after the GH infusion experiment (subsequent days) were measured in two separate assays. The intra- and interassay coefficients of variation for a plasma sample containing a GH concentration of 4.3 ng/ml were 5.1 and 17.9%, respectively.

Plasma IGF-I concentration was determined on samples collected every other hour. As recommended (Bang, 1995), a validation of the assay was performed. Seven plasma samples were obtained from pigs under various conditions to provide a wide range of IGF-I levels: plasma samples from pigs with increasing age (113 days of gestation, 26 and 180 days of age), from lactating sow and from weaned sow and pooled samples from GH-treated pigs and from feed-restricted pigs. Levels of IGF-I determined after an acid-ethanol extraction were compared to levels determined after a glycyl-glycine/G-50 extraction (Frey et al, 1994). Good parallelism between the IGF-I curve and dilution of plasma samples extracted by the two methods was observed. In agreement with previous findings in pigs (Frey et al, 1994), our data indicate that although the acid-ethanol extraction yielded IGF-I levels that were higher than those obtained for glycyl-glycine/G-50 extracted plasma, the correlation coefficient for all samples between the two methods was 0.97 ($P < 0.001$). The slope was 2.2 and the Y intercept was 41.2. Therefore, the plasma IGF-I concentrations were determined using a double antibody radioimmunoassay after an acid-ethanol extraction, as previously described by Daughaday et al (1980). The assay was performed using ^{125}I-IGF-I (Amersham, UK) as a tracer, recombinant bovine IGF-I as a standard and a polyclonal antibody raised in rabbit (Claus et al, 1992) and used at a final dilution of 1:30 000. Cross-reactivity with IGF-II was 1.7%. Samples from the same age group were analyzed within a single assay. The intra- and interassay coefficients of variation for a plasma sample containing 553 ng/ml of IGF-I were 12 and 18.9%, respectively.

Determination of plasma GH criteria

Each individual 8 h plasma GH profile (day 1) was separately analyzed for the determination of baseline GH levels and GH peaks, according to the procedure described by Merriam and Wachter (1982).

Data analyses

All data were expressed as mean ± SEM. The area under the GH curve was estimated from 0 to 6 h after starting GH infusion. The area under the IGF-I curve was determined from 0 to 71 h after the onset of the GH infusion by calculating the area included between the IGF-I curve and mean levels measured before GH infusion.

Data were analyzed by analysis of variance, using the generalized linear model of SAS (1989). The model included the main effects of breed and age, as well as the age x breed interaction. For the analyses of IGF-I profiles after GH infusion (repeated measurements of IGF-I), a split plot in time model was used, and the interactions with time were introduced into the model. When a significant age x breed interaction was observed, separate analyses were also conducted to test the significance of the effect of age within each breed and the significance of the effect of breed within each age. To further analyze the effect of developmental stage, 80-day-old MS pigs were compared to 185-day-old LW pigs.

RESULTS

Plasma GH and IGF-I levels in the absence of GH infusion

Mean plasma GH concentrations at 80 and 185 days of age were similar in both breeds (table I). However, MS pigs exhibited GH peaks of shorter duration ($P < 0.05$) than LW animals. Between 80 and 185 days of age, mean plasma GH concentrations decreased ($P < 0.001$) in both MS and LW pigs. In both breeds, this decrease was the result of a decline in baseline GH levels ($P < 0.05$), as well as in the amplitude ($P < 0.01$) and frequency ($P < 0.01$) of GH peaks. Eighty-day-old MS pigs exhibited higher ($P <$

Table I. Plasma growth hormone (GH) profile criteria and insulin-like growth factor-I (IGF-I) concentrations in Large White (LW) and Meishan (MS) pigs at 80 and 185 days of age (means ± SEM).

Breed	*Age (days)*	*Mean GH concentration (ng/ml)*	*Baseline GH concentration (ng/ml)*	*Duration of GH peaks (min)*	*Frequency of GH peaks (N/8 h)*	*Amplitude of GH peaks (ng/ml)*	*Mean IGF-I concentration (ng/ml)*
LW	80	4.67 ± 0.30	3.43 ± 0.43	80.6 ± 11.9	2.92 ± 0.52	7.26 ± 0.49	179 ± 18
	185	2.92 ± 0.24	2.52 ± 0.23	64.5 ± 12.7	1.97 ± 0.29	5.27 ± 0.56	356 ± 48
MS	80	4.15 ± 0.29	3.47 ± 0.34	48.3 ± 4.6	4.03 ± 0.36	6.53 ± 0.53	193 ± 35
	185	3.20 ± 0.31	2.89 ± 0.23	44.4 ± 6.4	2.33 ± 0.21	4.92 ± 0.56	222 ± 33
Significance of effects	Age	***	*	NS	**	**	**
	Breed	NS	NS	*	NS	NS	NS
	Age x breed	NS	NS	NS	NS	NS	*
Significance of difference between 80-day-old MS and 185-day-old LW pigs		**	*	NS	**	NS	*

NS: $P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

0.01) mean GH levels than 185-day-old LW pigs.

Plasma IGF-I concentrations were similar for both breeds at 80 days of age while they were lower ($P < 0.05$) in MS than in LW pigs at 185 days of age (table I). Plasma IGF-I concentrations increased ($P < 0.01$) with age in LW pigs, whereas the slight increase observed in MS pigs between 80 and 185 days of age was not significant. In addition, 80-day-old MS pigs exhibited a lower ($P < 0.05$) plasma IGF-I concentration than 185-day-old LW pigs (table I).

GH infusion in MS and LW pigs

Steady-state concentration of plasma GH was achieved within 1 h after the onset of the GH infusion (fig 1). Plasma GH concentrations returned to values close to baseline levels within 1 h after the infusion was stopped. Despite the infusion of somewhat lower doses (per kg) at 185 days of age, the area under the GH curve was higher at 185 days of age than at 80 days of age in both breeds (table II). In addition, the area under the GH curve was higher ($P < 0.01$) in

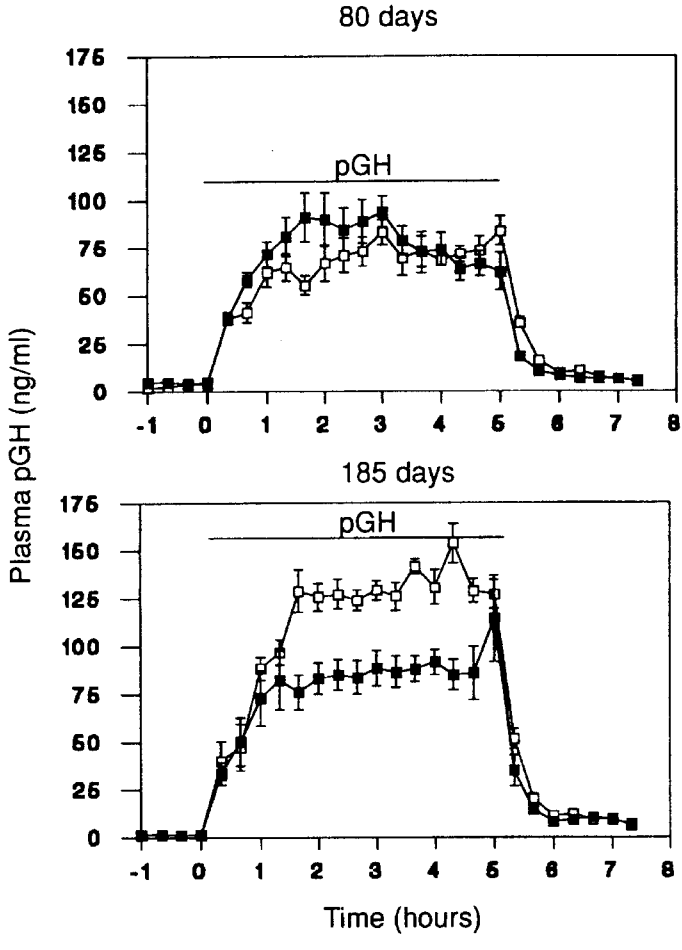

Fig 1. Plasma growth hormone (pGH) concentrations in Large White (□) and Meishan (■) pigs infused with GH at 80 and 185 days of age. Results are means ± SEM.

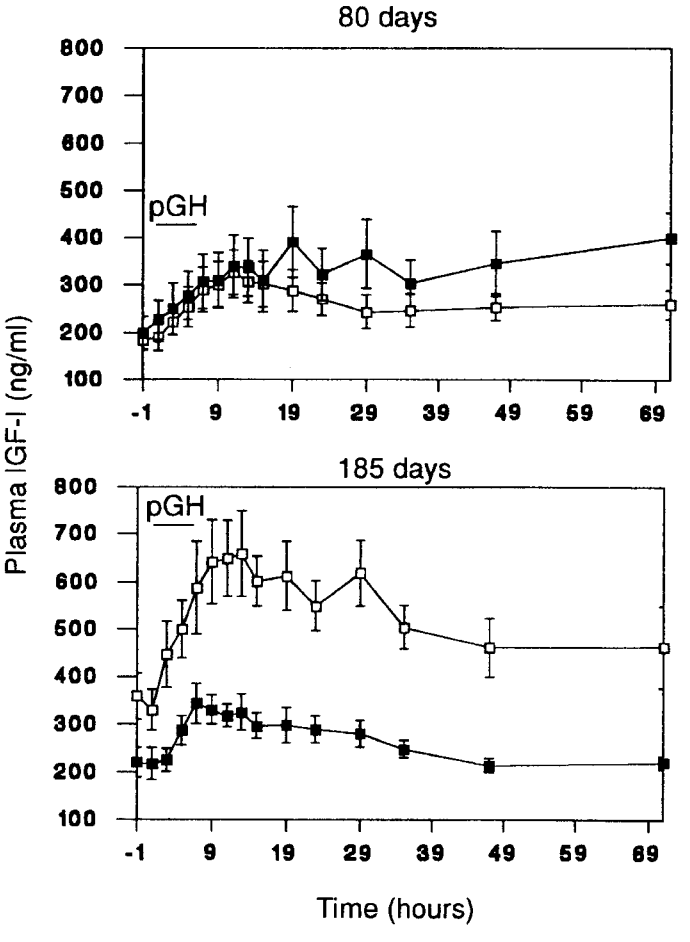

Fig 2. Plasma insulin-like growth factor-I (IGF-I) response to the infusion of growth hormone (GH) in Large White (□) and Meishan (■) pigs at 80 and 185 days of age. Results are means ± SEM.

LW than in MS pigs at 185 days of age. The area under the GH curve was lower ($P < 0.001$) in 80-day-old MS than in 185-day-old LW pigs.

IGF-I responses to GH in MS and LW pigs

GH infusion caused a rapid and persistent rise in plasma IGF-I concentration in both breeds (fig 2). In all four groups of pigs, IGF-I concentrations were significantly higher than preinfusion levels from 4 h (2 h in 80-day-old MS pigs) after the onset of the GH infusion. The rise in IGF-I concentration was significant until 36 h in 185-day-old MS and until the end of the sampling period in the three other groups (80-day-old MS and LW pigs at both ages). The area under the IGF-I curve increased with age ($P < 0.001$) in LW pigs, whereas it decreased ($P < 0.01$) in MS pigs (table II). The area under the IGF-I curve was greater ($P < 0.01$) in MS than in LW pigs at 80 days of age, whereas the reverse was observed at 185 days of age ($P < 0.001$). In addition, the area under the IGF-I curve was similar in 80-day-old MS and in 185-day-old LW pigs.

Table II. Growth hormone (GH) infusion data and insulin-like growth factor-I (IGF-I) response in Large White (LW) and Meishan (MS) pigs at 80 and 185 days of age (means ± SEM).

Breed	*Age (days)*	*Flow rate (ng x min^{-1} x kg^{-1})*	*Area under the GH curve (ng x min x L^{-1})*	*Area under the IGF-I curve (ng x h x L^{-1})*
LW	80	160 ± 4	20.9 ± 1.4	5.5 ± 1.2
	185	125 ± 4	35.9 ± 1.0	10.9 ± 1.4
MS	80	156 ± 5	22.8 ± 2.5	10.0 ± 2.0
	185	115 ± 1	25.2 ± 2.7	2.0 ± 1.4
Significance of effects	Age	***	***	NS
	Breed	NS	*	NS
	Age x breed	NS	**	***
Significance of difference between 80-day-old MS and 185-day-old LW pigs			***	NS

NS: $P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

DISCUSSION

The present study was designed to determine whether the slower growth of MS pigs could be due to an alteration of the GH/IGF-I axis. Mean plasma GH concentration decreased with age in both breeds as had been observed previously (Louveau et al, 1991). Despite a difference in duration of GH peaks, the mean plasma GH concentrations did not differ between the two breeds as had been reported at younger ages (Louveau et al, 1991). These data supported the absence of any obvious GH secretion deficiency in MS pigs. In accordance with previous works in pigs (Lee et al, 1991; Lamberson et al, 1995), the concentration of plasma IGF-I increased with age in LW pigs. At 80 days of age, plasma IGF-I concentrations did not differ between the two breeds in accordance with our previous observations taken between 10 and 150 days of age (Louveau et al, 1991). However, at 185 days of age, plasma IGF-I concentrations were lower in MS than in LW pigs. Lower IGF-I concentrations have also been observed in Yucatan micro and Hanford miniature pigs (Buonomo et al, 1987).

In both LW and MS pigs, the GH infusion increased plasma IGF-I levels in accordance with previous findings in pigs (Etherton et al, 1987; Sillence and Etherton, 1987; Owens et al, 1990) and sheep (Davis et al, 1992). However, the IGF-I response to the GH infusion was lower in LW than in MS pigs at 80 days of age, whereas the reverse was observed at 185 days of age. One can argue that it is difficult to interpret the IGF-I response to GH infusion because the area under the GH curve was higher in LW than in MS pigs at 185 days of age, although administered doses were similar. This observation may reflect a difference in the turnover of GH between LW and MS pigs at this age. Nevertheless, for similar area under the GH curve, it appears clearly that the IGF-I response to GH infusion was lower in 185-day-old than in 80-day-old MS pigs.

Because these comparisons are based on chronological ages, it may be argued that breed differences reflect the difference in stage of pubertal development. To our knowledge, there are few data regarding the development of changes in plasma GH and IGF-I levels during and after puberty in domestic animals. In man, sexual development is known to influence plasma GH and IGF-I levels. A surge in plasma GH (Rose et al, 1991) and IGF-I concentrations (Luna et al, 1983; Massa et al, 1992; Olivié et al, 1995) has been described during pubertal development. It is followed by a postpubertal decline in plasma GH and IGF-I concentrations (Corpas et al, 1993). In addition, it has been suggested that IGF-I levels are more closely associated with the pubertal stage than with chronological age in man (Olivié et al, 1995). As puberty occurs at about 8 months of age in LW pigs (Camous et al, 1985) compared to about 3 months of age in MS pigs (Prunier et al, 1993), 80-day-old MS females can be considered to be at a similar stage of sexual development (prepubertal) as 185-day-old LW females. However, the plasma IGF-I concentrations were lower in 80-day-old MS than in 185-day-old LW animals while the IGF-I response to GH was similar in the two breeds. This finding suggests that the difference between LW and MS pigs may not result only from the difference in stage of pubertal development. It also suggests that the developmental increase in IGF-I levels is less pronounced in MS than in LW pigs. It remains to establish whether IGF-I secretion is inhibited at younger ages in MS pigs due to their earlier sexual development. Alternatively, MS pigs might exhibit their full potential for IGF-I secretion earlier than the LW animals, so that IGF-I levels would then be similar at younger ages.

The finding of a lower plasma IGF-I concentration as well as a lower IGF-I response to GH in 185-day-old MS pigs than in LW pigs suggests the development of a GH resistance in MS pigs. This is in agreement with the observation of a GH resistance that develops with increasing age in man (Lieberman et al, 1994). The hypothesis of a decreased number of GH receptors can be ruled out because a recent study performed in our laboratory (Schnoebelen-Combes et al, 1996) demonstrated that hepatic GH receptor levels are similar in LW and MS pigs at 180 days of age. The presence of a lower IGF-I concentration in MS than in LW pigs despite similar levels of GH receptor suggests an impairment of the GH receptor signal transduction as it has been described in man with aging (Xu et al, 1995).

In conclusion, whereas the plasma IGF-I concentrations and IGF-I response to GH were similar or higher in MS than in LW pigs at 80 days of age, they were lower in MS than in LW pigs at 185 days of age. The development of GH resistance in MS pigs is likely associated with sexual maturity, as suggested by a similar IGF-I response to GH in animals considered to be at the same pubertal stage. Whether such GH resistance would also be observed in postpubertal LW female pigs remains to be investigated. Nevertheless, the presence of lower IGF-I concentrations in MS than in LW animals at the same stage of sexual development suggests that the maximum potential for IGF-I secretion, exhibited around puberty, could be lower in MS than in LW animals.

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