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The cortisol response to ACTH in pigs, heritability and influence of corticosteroid-binding globulin

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In the search for biological basis of robustness, this study aimed (i) at the determination of the heritability of the cortisol response to ACTH in juvenile pigs, using restricted maximum likelihood methodology applied to a multiple trait animal model, and (ii) at the study of the relationships between basal and stimulated cortisol levels with corticosteroid-binding globulin (CBG), IGF-I and haptoglobin, all important players in glucose metabolism and production traits. At 6 weeks of age, 298 intact male and female piglets from 30 litters (30 dams and 30 boars) were injected with 250 μg ACTH(1–24) (Synacthen). Blood was taken before ACTH injection to measure basal levels of cortisol, glucose, CBG, IGF-I and haptoglobin, and 60 min later to measure stimulated cortisol levels and glucose. Cortisol increased 2.8-fold after ACTH injection, with a high correlation between basal and stimulated levels (phenotypic correlation, $r_p = 0.539$; genetic correlation, $r_g = 0.938$). Post-ACTH cortisol levels were highly heritable ($h^2 = 0.684$) and could therefore be used for genetic selection of animals with a more reactive hypothalamic–pituitary–adrenocortical axis. CBG binding capacity correlated with cortisol levels measured in basal conditions in males only. No correlation was found between CBG binding capacity and post-ACTH cortisol levels. Basal IGF-I concentration was positively correlated with BW at birth and weaning, and showed a high correlation with CBG binding capacity with a strong sexual dimorphism, the correlation being much higher in males than in females. Basal haptoglobin concentrations were negatively correlated with CBG binding capacity and IGF-I concentrations. Complex relationships were also found between circulating glucose levels and these different variables that have been shown to be related to glucose resistance in humans. These data are therefore valuable for the genetic selection of animals to explore the consequences on production and robustness traits, but also point at pigs as a relevant model to explore the underlying mechanisms of the metabolic syndrome including the contribution of genetic factors.

Keywords: ACTH stimulation test, cortisol, CBG, robustness, pig

Implications

The adrenocortical axis, the main stress-responsive neuroendocrine system, is strongly influenced by genetic factors, as shown here with the cortisol response to ACTH in pigs. This response will be used to select animals with a stronger stress response and study the consequences on production and robustness traits.

Introduction

Adrenal hormones, essential for survival, play important roles in metabolism regulation, immunity, reproduction, water and salt balance and various brain functions, as well as in stress responses. A hyperactive or hyper-reactive hypothalamic–pituitary–adrenocortical (HPA) axis has an unfavorable effect on production traits such as growth rate and feed efficiency (Hennessy and Jackson, 1987) or body composition with an increased lipids/proteins ratio (Foury *et al.*, 2005 and 2007). A few studies established a positive relationship between HPA axis activity and robustness traits such as newborn survival, heat tolerance and resistance to diseases (see Mormede *et al.*, 2011b and Mormede and

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Terenina, 2012, for review). It has been shown in several species that the HPA axis activity has been largely reduced during the domestication process (e.g. Weiler *et al.*, 1998 in pigs) and more recently by selection for production traits (Foury *et al.,* 2009). This decrease in adrenocortical axis activity may partly explain the compromised robustness that coincides with over-focused genetic improvement of production traits in farm animals. The large individual variation in HPA axis activity and reactivity, and the importance of genetic factors are well documented (Kadarmideen and Janss, 2007; Mormede *et al.*, 2011a). We have therefore hypothesized that genetic selection for a more active HPA axis activity could improve robustness (Mormede *et al.*, 2011b; Mormede and Terenina, 2012).

The adrenal sensitivity to ACTH is an important factor regulating cortisol production. In pigs as in humans, the cortisol response to ACTH was shown to differ largely among individuals but to be stable through time (Hennessy *et al.*, 1988) and extensive functional exploration showed that a large part of the variability in the cortisol response to ACTH is due to differential sensitivity of the adrenal gland to ACTH (Hennessy, 1986; Zhang *et al.*, 1990). Although the cortisol response to ACTH can be influenced by the life history of the animals, the role of genetic factors is shown by differences between genetic stocks in pigs (Desautes *et al.*, 1997) and several other species (see Mormede and Terenina, 2012 for review). Selected lines of chickens could be established on the basis of their corticosterone response to ACTH (Edens and Siegel, 1975). Therefore, the adrenal response to ACTH could be an efficient phenotype for a genetic selection of a more active HPA axis.

The aim of this study was to estimate the genetic variability of cortisol secretion in response to ACTH stimulation in pigs. In the same samples were also measured the levels of several endocrine parameters related to HPA axis: corticosteroid-binding globulin (CBG), as a regulator of blood cortisol concentration (Moisan, 2010 and 2013), glucose and IGF-I as representatives of metabolic action of cortisol (Mazziotti and Giustina, 2013), and haptoglobin for inflammatory processes (Heegaard *et al.*, 2011).

Material and methods

All animal experiments were conducted according to the INRA Quality Reference System, and to relevant French (Directive 87/148, Ministère de l'Agriculture et de la Pêche) and international (Directive 2010/63/EU, European Community) legislation. They adhered to protocols approved by Région Aquitaine Veterinary Services (approval ID: 33 00681).

Animals

A total of 30 Large White sows bred in an INRA experimental farm were inseminated each once with semen from 30 Large White boars. This design was chosen to obtain a G0 generation with a maximal genetic diversity for divergent selection based on the cortisol response to ACTH. A total of 298 intact male and female piglets were weaned at the age of 4 weeks and studied at 6 weeks, in four successive experimental batches. They received food and water *ad libitum*. Starter diet (18.6% protein and 10.8 MJ/kg net energy (NE) on a dry matter basis) was given during the last week before and the first 2 weeks after weaning and weaner diet (17.5% protein and 10.0 MJ/kg NE) was given from the 2nd week after weaning on. All piglets were weighed at birth and at weaning.

Experimental protocol

Experiments were done in the morning (0800 to 1200 h). An initial blood sample was collected in tubes with sodium heparin (Vacutainer®, Becton-Dickinson, Le Pont de Claix, France) by direct puncture from the jugular vein, the piglets being maintained on their back by light restraint. The procedure does not take more than 30 s after catching the animal in the pen. Piglets were then injected in the neck muscles with mammalian ACTH(1–24) (Immediate Synacten; Novartis, Rueil-Malmaison, France) at the dose of 250 μg/animal and put back in their pen. A second blood sample was collected 1 h after ACTH injection. The blood samples were centrifuged and plasma frozen at −80°C until assay. The dose of ACTH was chosen to be maximally stimulating the adrenal cortex. The time for blood collection after ACTH injection (1 h) corresponds to the peak of the response (Hennessy *et al.*, 1988).

Biological assays

Plasma total cortisol was measured using a specific direct radio immunoassay (RIA) (GammaCoat™ Cortisol; DiaSorin, Antony, France). The CBG capacity to bind cortisol was measured by radiocompetitive binding after concanavallin A – sepharose extraction as described (Pugeat *et al.*, 1984; Ousova *et al.*, 2004). Glucose was measured by spectrophotometry with the glucose oxidase technique. The plasma concentration of haptoglobin was measured using a colorimetric method and haptoglobin assay kit based on binding of haptoglobin to hemoglobin (Tridelta Ltd, Maynooth, Co. Kildare, Ireland). Plasma IGF-I concentration was measured using a double-antibody RIA (Louveau and Bonneau, 1996) after an acid–ethanol extraction. CBG, haptoglobin and IGF-I concentrations were measured in basal blood samples only.

Statistical analyses

Normality of distribution was analyzed with the Shapiro and Wilk test. Despite significant departures from normality, all biological variables except glucose levels were transformed to their logarithmic scores. A linear model (GLM procedure; SAS Institute Inc., Cary, NC, USA) was used to study the fixed effects of batch and sex. Birth and weaning weights were also tested as covariates in two different models. In addition, the Pearson correlations were estimated between variables and both birth and weaning weights, after correction for batch and sex effects. Residual Pearson correlations among variables, after correction for batch effect and birth or weaning weight, were calculated. Correlations were estimated with the CORR procedure (SAS) and compared between males and females with the Fisher's *z* transformation.

Data are given as arithmetic means ± SD. Significance threshold was set at $P < 0.05$.

Genetic parameters were estimated using restricted maximum likelihood methodology applied to a multiple trait animal model, with the VCE6 software (Neumaier and Groeneveld, 1998). The model of analysis included the effect of batch and sex, and animal additive effect as a random effect. Random effect of litter was estimated. The part of variance estimated for this effect was low thus litter effect was removed from the final analysis. Pedigree, up to six generations of ancestors for both sires and dams, included a total of 1556 animals. Owing to lack of precision for genetic parameter estimation, only results for cortisol and CBG are reported here.

Results

Descriptive statistics are given in Table 1 and Pearson correlations by sex in Table 2.

Table 1 *Descriptive statistics*

					Correlation	
Variable	Unit	*n*	Mean and SD	Sex	BW_birth	BW_weaning
Cortisol_B	nmol/l	298	103 ± 45	**		
Cortisol_A	nmol/l	298	267 ± 65	ns		
CBG	nmol/l	295	11.5 ± 4.8	**		
Glucose_B	g/l	298	1.20 ± 0.13	****		
Glucose_A	g/l	298	1.06 ± 0.16	***	0.203***	
IGF-I	ng/ml	297	33.5 ± 20.8	**	0.219****	0.250****
Haptoglobin	g/l	298	0.699 ± 0.710	ns		0.154**
BW_birth	g	298	1395 ± 299			
BW_weaning	g	297	8662 ± 1568			

CBG = corticosteroid-binding globulin.
Variables: the letter B refers to basal and A to post-ACTH values.
Correlation coefficient of variables corrected for fixed effects (batch and sex) with BW at birth and weaning.
ns = $P>0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$.

As expected, plasma cortisol concentration increased after ACTH injection (2.8-fold, $P < 0.0001$). The effect of sex ($P = 0.02$) and the sex × treatment interaction ($P < 0.05$) were also significant. Although basal levels were slightly higher in males (107 ± 44 *v.* 98 ± 46 nmol/l; $P < 0.01$), the sex difference was no longer significant after ACTH injection (267 ± 65 nmol/l). Plasma cortisol concentrations measured before and after ACTH were highly correlated ($r = 0.539$; $P < 0.0001$), with no sex difference (Table 2 and Figure 1). CBG binding capacity measured in basal samples was higher in females (12.7 ± 5.6 *v.* 10.5 ± 4.0 nmol/l, $P < 0.01$). Basal cortisol levels were positively correlated with CBG in males ($r = 0.424$, $P < 0.0001$) but not in females ($r = 0.067$), and these correlation coefficients were different ($P = 0.001$). The correlation between CBG and cortisol levels after ACTH was not significant ($r = 0.028$). There was no significant correlation of cortisol and CBG binding capacity with BW at birth or at weaning (Table 1). The values of the variance and covariance components for cortisol and CBG levels are given in Table 3. A high heritability value was estimated for cortisol concentration after ACTH ($h^2 = 0.68 \pm 0.12$), as compared with basal cortisol levels ($h^2 = 0.36 \pm 0.09$) and CBG binding capacity ($h^2 = 0.19 \pm 0.06$). A high genetic correlation was also estimated between basal and post-ACTH cortisol levels ($r_g = 0.94 \pm 0.04$).

Plasma glucose concentrations were higher in males (1.26 ± 0.11 *v.* 1.15 ± 0.13 g/l; $P < 0.0001$) and decreased after ACTH injection (1.10 ± 0.16 g/l in males *v.* 1.03 ± 0.16 g/l in females, $P < 0.0001$) with a significant sex × treatment interaction ($P < 0.005$, the decrease being less important in females). Pre- and post-ACTH glucose concentrations were highly correlated with no significant sex difference ($r = 0.489$, $P < 0.0001$). Cortisol and glucose concentrations were moderately correlated in basal conditions ($r = 0.240$, $P < 0.0001$) but not after ACTH ($r = 0.032$).

Table 2 *Phenotypic correlations among variables*

	Cortisol_B	Cortisol_A	CBG	Glucose_B	Glucose_A	IGF-I	Haptoglobin
Cortisol_B		*0.531*	***0.067***	*0.254*	*0.235*	0.088	0.002
		<0.0001	***0.421***	*0.002*	*0.004*	0.286	0.977
Cortisol_A	*0.506*		−0.033	0.138	0.100	−0.106	0.112
	<0.0001		0.694	0.096	0.225	0.201	0.176
CBG	***0.424***	0.115		0.158	0.149	***0.248***	*−0.257*
	<0.0001	0.161		0.056	0.073	***0.003***	*0.002*
Glucose_B	*0.230*	0.042	*0.176*		*0.474*	*0.409*	0.003
	0.005	0.613	*0.032*		*<0.0001*	*<0.0001*	0.969
Glucose_A	0.110	−0.106	0.103	*0.566*		*0.374*	−0.065
	0.182	0.195	0.210	*<0.0001*		*<0.0001*	0.430
IGF-I	*0.217*	−0.109	***0.412***	*0.289*	*0.383*		*−0.192*
	0.008	0.186	***<0.0001***	*<0.001*	*<0.0001*		*0.020*
Haptoglobin	−0.041	*0.176*	*−0.206*	0.024	0.083	*−0.299*	
	0.617	*0.031*	*0.012*	0.772	0.314	*<0.001*	

CBG = corticosteroid-binding globulin.
Variables: the letter B refers to basal and A to post-ACTH values.
Pearson correlation coefficients on the first line and *P* values on the second line. Females ($n = 146$ to 148) over and males ($n = 149$ to 150) under the diagonal. Significant correlations in italics; coefficients of correlation significantly different between males and females in boldface. These parameters were computed after correction for significant fixed effects, batch for all variables, BW at weaning for haptoglobin and BW at birth for glucose_A and IGF-I.

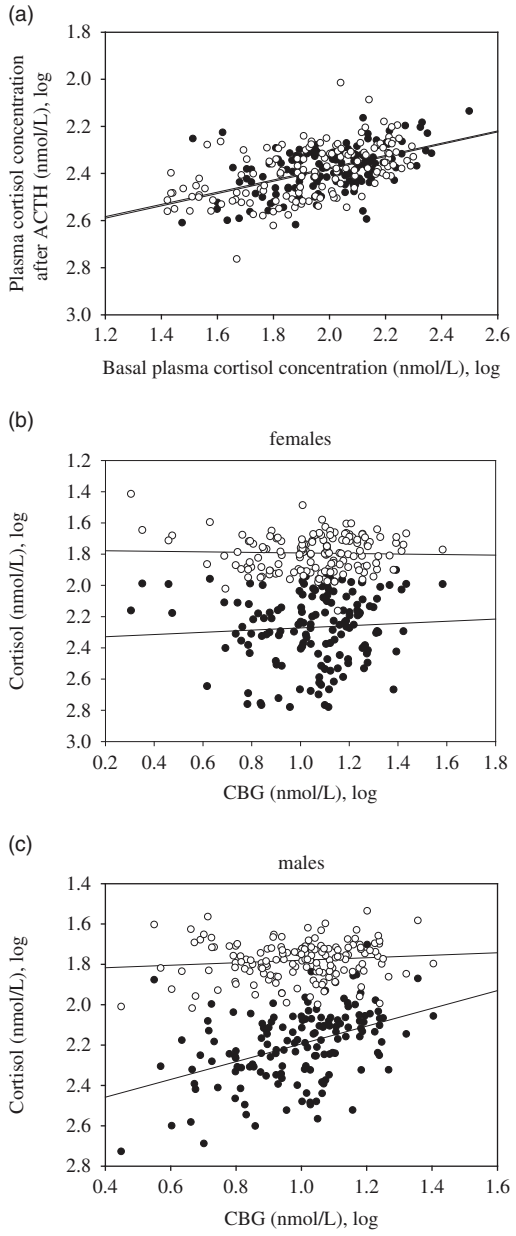

Figure 1 Observed associations between plasma cortisol concentrations measured before and after ACTH injection (a; white dots, females and black dots, males), and between plasma cortisol concentration and CBG binding activity in females (b) and males (c; black dots, before and white dots, after ACTH injection). All axes in log scale. CBG = corticosteroid-binding globulin.

Table 3 *Additive and residual variances (on the diagonal) and covariances (above the diagonal) for cortisol before and after ACTH injection and CBG levels*

	Cortisol_B	Cortisol_A	CBG
Additive (co)variances	0.01603	0.01057	−0.00131
		0.00788	0.00025
			0.00742
Residual (co)variances	0.02899	0.00955	0.00169
		0.03204	0.00030
			0.00364

CBG = corticosteroid-binding globulin.

Plasma IGF-I concentrations were higher in males (39.3 ± 21.7 *v.* 28.3 ± 19.6 ng/ml) and positively correlated with circulating glucose concentrations before ($r = 0.327$, $P < 0.0001$) and after ($r = 0.321$, $P < 0.0001$) ACTH injection, with no significant sex difference. IGF-I concentrations showed a high correlation with CBG binding capacity with a strong sexual dimorphism ($P = 0.001$), the correlation being much higher in males ($r = 0.412$, $P < 0.0001$) than in females ($r = 0.248$, $P = 0.003$). IGF-I concentrations were also correlated with BWs at birth and weaning (Table 1). Haptoglobin concentrations were not influenced by sex and BW at birth but positively correlated with BW at weaning (Tables 1 and 2); they were negatively correlated with CBG binding capacity ($r = -0.236$, $P < 0.0001$).

Discussion

In the present family study in Large White pigs, we show that the heritability of post-ACTH cortisol concentration in plasma is very high, and the strong genetic correlation between basal and post-ACTH plasma cortisol concentrations shows that the same genetic factors regulate individual differences in cortisol concentrations in these two states. Various results have been obtained on the relationships between CBG binding activity and plasma cortisol levels in pigs, depending on the genetic type (Geverink *et al.*, 2006). We show here that sex is an important factor to consider and that post-ACTH cortisol levels are independent from CBG. Other factors like age should also be studied more thoroughly (Roberts *et al.*, 2003).

We show here that IGF-I levels measured at 6 weeks are correlated with BW at birth and at weaning. In humans, both fetal and neonatal IGF-I circulating levels are correlated with BW (Lassarre *et al.*, 1991). The reciprocal interactions between the GH/IGF and the HPA axis are well documented (Neggers and van der Lely, 2011; Mazziotti and Giustina, 2013), including during fetal development (Braun *et al.*, 2013), but little is known on the relationships between cortisol and IGF-I in juvenile pigs. We show here that CBG may play an important role in these relationships with a strong sex difference. Indeed, the correlation between cortisol and IGF-I concentrations was significant in basal samples in males only (just like the correlation between cortisol concentrations and CBG binding activity) and the correlation between IGF-I concentrations and CBG binding activity was much higher than with cortisol concentrations in males than in females. Sex differences in HPA axis activity and response to stress has been documented previously in juvenile pigs (e.g. Cooper *et al.*, 2009) but their biological mechanisms have not been thoroughly investigated. It is worth noting, however, that several authors have shown that the HPA axis activity was shaped by prenatal influences in a sex-specific manner (Kanitz *et al.*, 2006; Kranendonck *et al.*, 2008; Collier *et al.*, 2011; Óvilo *et al.*, 2014).

Both cortisol and IGF-I are important components of glucose metabolism regulation (Dallman *et al.*, 2007;

Berryman *et al.*, 2013). Several clinical studies have shown a relationship between CBG levels or CBG gene polymorphisms and metabolic parameters related to insulin resistance syndrome (e.g. Fernandez-Real *et al.*, 2002; Barat *et al.*, 2005; Richard *et al.,* 2009), and the CBG locus has been shown to be linked with metabolic traits in several studies (see Moisan, 2010 and Mormede *et al.*, 2011a and 2011b for review), including in pigs (Desautes *et al.*, 2002; Ousova *et al.*, 2004), and we showed previously that CBG was a better predictor of carcass composition than cortisol levels (Ousova *et al.*, 2004). In most cases, the physiological effects of CBG have been interpreted as resulting from the influence of CBG on the level and bioavailability of cortisol (Perogamvros *et al.*, 2012; Moisan, 2013). The precise interplay between these different parameters and the mechanisms of CBG influence on metabolic parameters remains to be explored.

Haptoglobin is a positive acute phase protein, which levels increase in response to pro-inflammatory situations such as microbial challenges (Heegaard *et al.*, 2011) and poor environmental sanitary conditions (Pastorelli *et al.*, 2012). Apart from immune stimuli, haptoglobin can also be released in response to other stressors like hot ambient temperature (Heo *et al.*, 2005), transport (Piñeiro *et al.*, 2007b) or unpredictable feeding practices (Piñeiro *et al.*, 2007a). In the present study, haptoglobin levels were unrelated to cortisol levels. Interestingly, they were negatively correlated with CBG levels. It is noteworthy that CBG, which is a protein of hepatic origin like positive and negative acute phase proteins, displays reduced concentrations in cases of inflammatory conditions (Garrel, 1996), and thus varies in the opposite way to haptoglobin. These opposite variations have also been observed in pigs, in inflammatory (Carroll *et al.*, 2003) as well as in other stressful conditions (Heo *et al.*, 2005; Piñeiro *et al.*, 2007a and 2007b).

Conclusion

The plasma cortisol response to ACTH in juvenile pigs is highly heritable and could therefore be used to select animals with a more active HPA axis, independently from CBG binding capacity. Although plasma CBG binding capacity is correlated only with basal cortisol levels in males, it plays a critical role in the network between the HPA axis and its metabolic (IGF-I, glucose) and innate immune system (haptoglobin) targets. A system genetics approach will be necessary to understand the relationships between these metabolic endocrine components and production traits in pigs as well as the metabolic syndrome in humans.

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References

Barat P, Duclos M, Gatta B, Roger P, Mormede P and Moisan MP 2005. Corticosteroid binding globulin gene polymorphism influences cortisol driven fat distribution in obese women. Obesity Research 13, 1485–1490.

Berryman DE, Glad CAM, List EO and Johannsson G 2013. The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nature Review Endocrinology 9, 346–356.

Braun T, Challis JR, Newnham JP and Sloboda DM 2013. Early-life glucocorticoid exposure: the hypothalamic-pituitary-adrenal axis, placental function, and long-term disease risk. Endocrine Reviews 34, 885–916.

Carroll JA, Gaines AM, Spencer JD, Allee GL, Kattesh HG, Roberts MP and Zannelli ME 2003. Effect of menhaden fish oil supplementation and lipopolysaccharide exposure on nursery pigs. I. Effects on the immune axis when fed diets containing spray-dried plasma. Domestic Animal Endocrinology 24, 341–351.

Collier CT, Williams PN, Carroll JA, Welsh TH and Laurenz JC 2011. Effect of maternal restraint stress during gestation on temporal lipopolysaccharide-induced neuroendocrine and immune responses of progeny. Domestic Animal Endocrinology 40, 40–50.

Cooper TA, Roberts MP, Kattesh HG and Kojima CJ 2009. Effects of transport stress, sex, and weaning weight on postweaning performance in pigs. Professional Animal Scientist 25, 189–194.

Dallman MF, Akana SF, Pecoraro NC, Warne JP, la Fleur SE and Foster MT 2007. Glucocorticoids, the etiology of obesity and the metabolic syndrome. Current Alzheimer Research 4, 199–204.

Desautes C, Bidanel JP, Milan D, Iannuccelli N, Amigues Y, Bourgeois F, Caritez JC, Renard C, Chevalet C and Mormede P 2002. Genetic linkage mapping of quantitative trait loci for behavioral and neuroendocrine stress response traits in pigs. Journal of Animal Science 80, 2276–2285.

Desautes C, Bidanel JP and Mormede P 1997. Genetic study of behavioral and pituitary-adrenocortical reactivity in response to an environmental challenge in pigs. Physiology and Behavior 62, 337–345.

Edens FW and Siegel HS 1975. Adrenal responses in high and low ACTH response lines of chickens during acute heat stress. General and Comparative Endocrinology 25, 64–73.

Fernandez-Real JM, Pugeat M, Grasa M, Broch M, Vendrell J, Brun J and Ricart W 2002. Serum corticosteroid-binding globulin concentration and insulin resistance syndrome: a population study. Journal of Clinical Endocrinology and Metabolism 87, 4686–4690.

Foury A, Devillers T, Sanchez MP, Griffon H, Le Roy P and Mormede P 2005. Stress hormones, carcass composition and meat quality in Large White x Duroc pigs. Meat Science 69, 703–707.

Foury A, Geverink NA, Gil M, Gispert M, Hortos M, Furnols MFI, Carrion D, Blott SC, Plastow GS and Mormede P 2007. Stress neuroendocrine profiles in five pig breeding lines and the relationship with carcass composition. Animal 1, 973–982.

Foury A, Tribout T, Bazin C, Billon Y, Bouffaud M, Gogué JM, Bidanel JP and Mormede P 2009. Estimation of genetic trends from 1977 to 2000 for stress-responsive systems in French large white and landrace pig populations using frozen semen. Animal 3, 1681–1687.

Garrel DR 1996. Corticosteroid-binding globulin during inflammation and burn injury: nutritional modulation and clinical implications. Hormone Research 45, 245–251.

Geverink NA, Foury A, Plastow GS, Gil M, Gispert M, Hortos M, Furnols MFI, Gort G and Moisan MP 2006. Cortisol-binding globulin and meat quality in five European lines of pigs. Journal of Animal Science 84, 204–211.

Heegaard PMH, Stockmarr A, Piñeiro M, Carpintero R, Lampreave F, Campbell FM, Eckersall PD, Toussaint MJM, Gruys E and Sorensen NS 2011. Optimal combinations of acute phase proteins for detecting infectious disease in pigs. Veterinary Research 42, 50.

Hennessy DP 1986. Metabolic clearance rate of cortisol in pigs: relationship to adrenal responsiveness. Research in Veterinary Science 41, 361–364.

Hennessy DP and Jackson PN 1987. Relationship between adrenal responsiveness and growth rate, Manipulating Pig Production: proceedings of the Inaugural Conference of the Australasian Pig Science Association (A.P.S.A.), 23–25 November, Albury, NSW, Australia, pp. 23.

Hennessy DP, Stelmasiak T, Johnston NE, Jackson PN and Outch KH 1988. Consistent capacity for adrenocortical response to ACTH administration in pigs. American Journal of Veterinary Research 49, 1276–1283.

Heo J, Kattesh HG, Roberts MP, Morrow JL, Dailey JW and Saxton AM 2005. Hepatic corticosteroid-binding globulin (CBG) messenger RNA expression and plasma CBG concentrations in young pigs in response to heat and social stress. Journal of Animal Science 83, 208–215.

Kadarmideen HN and Janss LLG 2007. Population and systems genetics analyses of cortisol in pigs divergently selected for stress. Physiological Genomics 29, 57–65.

Kanitz E, Otten W and Tuchscherer M 2006. Changes in endocrine and neurochemical profiles in neonatal pigs prenatally exposed to increased maternal cortisol. Journal of Endocrinology 191, 207–220.

Kranendonk G, Mulder EJH, Parvizi N and Taverne MAM 2008. Prenatal stress in pigs: experimental approaches and field observations. Experimental and Clinical Endocrinology & Diabetes 116, 413–422.

Lassarre C, Hardouin S, Daffos F, Forestier F, Frankenne F and Binoux M 1991. Serum insulin-like growth factors and insulin-like growth factor binding proteins in the human fetus. Relationships with growth in normal subjects and in subjects with intrauterine growth retardation. Pediatric Research 29, 219–225.

Louveau I and Bonneau M 1996. Effect of a growth hormone infusion on plasma insulin-like growth factor-I in Meishan and Large White pigs. Reproduction, Nutrition, Development 36, 301–310.

Mazziotti G and Giustina A 2013. Glucocorticoids and the regulation of growth hormone secretion. Nature Reviews Endocrinology 9, 265–276.

Moisan MP 2010. Genotype-phenotype associations in understanding the role of corticosteroid-binding globulin in health and disease animal models. Molecular and Cellular Endocrinology 316, 35–41.

Moisan MP 2013. CBG: a cortisol reservoir rather than a transporter. Nature Reviews Endocrinology 9, 78.

Mormede P, Foury A, Barat P, Corcuff JB, Terenina E, Marissal-Arvy N and Moisan MP 2011a. Molecular genetics of hypothalamic-pituitary-adrenal axis activity and function. Annals of the New York Academy of Science 1220, 127–136.

Mormede P, Foury A, Terenina E and Knap PW 2011b. Breeding for robustness: the role of cortisol. Animal 5, 651–657.

Mormede P and Terenina E 2012. Molecular genetics of the adrenocortical axis and breeding for robustness. Domestic Animal Endocrinology 43, 116–131.

Neggers SJCMM and van der Lely AJ 2011. Modulation of glucocorticoid metabolism by the GH-IGF-I axis. Endocrine Development 20, 181–186.

Neumaier A and Groeneveld E 1998. Restricted maximum likelihood estimation of covariances in sparse linear models. Genetics, Selection, Evolution 30, 3–26.

Ousova O, Guyonnet-Duperat V, Iannuccelli N, Bidanel JP, Milan D, Genet C, Llamas B, Yerle M, Gellin J, Chardon P, Emptoz-Bonneton A, Pugeat M, Mormede P and Moisan MP 2004. Corticosteroid binding globulin: a new target for cortisol-driven obesity. Molecular Endocrinology 18, 1687–1696.

Óvilo C, González-Bulnes A, Benítez R, Ayuso M, Barbero A, Pérez-Solana ML, Barragan C, Astiz S, Fernandez A and López-Bote C 2014. Prenatal programming in an obese swine model: sex-related effects of maternal energy restriction on morphology, metabolism and hypothalamic gene expression. The British Journal of Nutrition 111, 735–746.

Pastorelli H, Le Floc'h N, Merlot E, Meunier-Salaün MC, van Milgen J and Montagne L 2012. Sanitary housing conditions modify the performance and behavioural response of weaned pigs to feed- and housing-related stressors. Animal 6, 1811–1820.

Perogamvros I, Ray DW and Trainer PJ 2012. Regulation of cortisol bioavailability – effects on hormone measurement and action. Nature Reviews Endocrinology 8, 717–727.

Piñeiro C, Piñeiro M, Morales J, Carpintero R, Campbell FM, Eckersall PD, Toussaint MJM, Alava MA and Lampreave F 2007a. Pig acute-phase protein levels after stress induced by changes in the pattern of food administration. Animal 1, 133–139.

Piñeiro M, Piñeiro C, Carpintero R, Morales J, Campbell FM, Eckersall PD, Toussaint MJM and Lampreave F 2007b. Characterisation of the pig acute phase protein response to road transport. The Veterinary Journal 173, 669–674.

Pugeat MM, Chrousos GP, Nisula BC, Loriaux DL, Brandon D and Lipsett MB 1984. Plasma cortisol transport and primate evolution. Endocrinology 115, 357–361.

Richard E, Fernandez-Real JM, Lopez-Bermejo A, Ricart W, Dechaud H, Pugeat M and Moisan MP 2009. Corticosteroid binding globulin and glucocorticoid receptor genotypes influence body composition in a male population. International Journal of Genetics and Molecular Biology 1, 59–63.

Roberts MP, Kattesh HG, Baumbach GA, Gillespie BE, Godkin JD, Schneider JF and Saxton AM 2003. Age-related changes in porcine corticosteroid-binding globulin (pCBG) as determined by an enzyme-linked immunosorbent assay. Domestic Animal Endocrinology 24, 323–339.

Weiler U, Claus R, Schnoebelen-Combes S and Louveau I 1998. Influence of age and genotype on endocrine parameters and growth performance: a comparative study in Wild boars, Meishan and Large White boars. Livestock Production Science 54, 21–31.

Zhang SH, Hennessy DP and Cranwell PD 1990. Pituitary and adrenocortical responses to corticotropin-releasing factor in pigs. American Journal of Veterinary Research 51, 1021–1025.