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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.

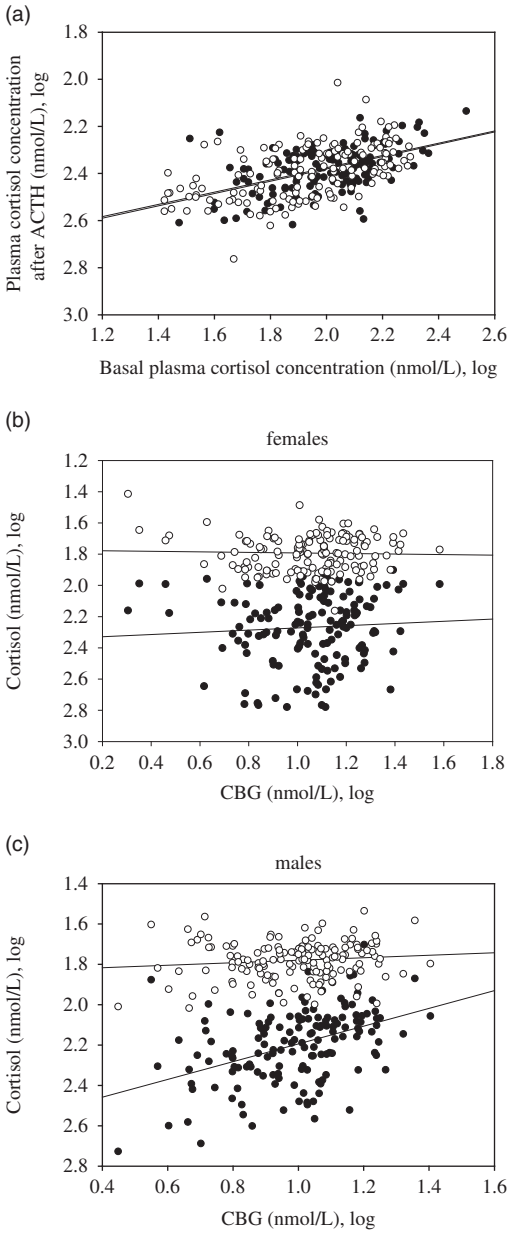

Figure 1 Observed associations between plasma cortisol concentrations measured before and after ACTH injection (a; white dots, females and black dots, males), and between plasma cortisol concentration and CBG binding activity in females (b) and males (c; black dots, before and white dots, after ACTH 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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