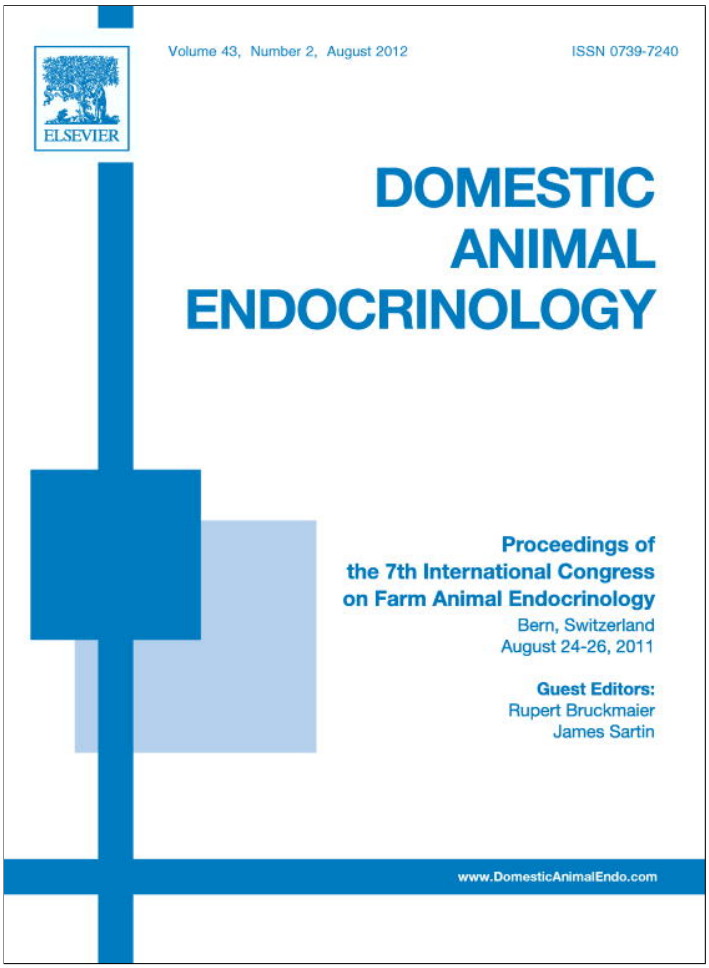


Available online at www.sciencedirect.com

SciVerse ScienceDirect

Domestic Animal Endocrinology 43 (2012) 116–131

DOMESTIC ANIMAL ENDOCRINOLOGY

www.domesticanimalendo.com

Molecular genetics of the adrenocortical axis and breeding for robustness

P. Mormede*, E. Terenina

INRA, UMR 444 Génétique Cellulaire, F-31326 Castanet-Tolosan, France

Received 3 February 2012; received in revised form 20 April 2012; accepted 14 May 2012

Abstract

The concept of robustness refers to the combination of a high production potential and a low sensitivity to environmental perturbations. The importance of robustness-related traits in breeding objectives is progressively increasing toward the production of animals with a high production level in a wide range of climatic conditions and production systems, together with a high level of animal welfare. Current strategies to increase robustness include selection for "functional traits," such as skeletal and cardiovascular integrity, disease resistance, and mortality at various stages. It is also possible to use global evaluation of sensitivity to the environment (eg reaction norm analysis or canalization), but these techniques are difficult to implement in practice. The glucocorticoid hormones released by the adrenal cortex exert a wide range of effects on metabolism, the cardiovascular system, inflammatory processes, and brain function, for example. Protein catabolism toward energy production and storage (lipids and glycogen) supports their pivotal role in stress responses aiming at the adaptation and survival of individuals under strong environmental pressure. Large individual variations have been described in adrenocortical axis activity, with important physiopathological consequences. In terms of animal production, higher cortisol levels have negative effects on growth rate and feed efficiency and increase the fat:lean ratio of carcasses. On the contrary, cortisol has positive effects on functional traits and adaptation. Intense selection for lean tissue growth and more generally high protein output during the past decades has concomitantly reduced cortisol production, which may be responsible for the negative effects of selection on functional traits. In this paper, we review experimental evidence suggesting that the balance between production and functional traits was modified in favor of improved robustness by selecting animals with higher adrenocortical axis activity, as well as the molecular genetic tools that can be used to fine-tune this objective.

Keywords: Stress; Adaptation; Welfare; Cortisol; Functional traits; Genomic selection

1. Introduction: The new challenges to breeding food-producing animals

In its "Sustainable Farm Animal Breeding and Reproduction, a vision for 2025," the European FABRE Technology Platform described the farm animal of the future as "robust, adapted and healthy" and "producing a safe and healthy food" (2006; http://www.euroqualityfiles.net/vision_pdf/vision_fabre.pdf). Intense genetic selection of farm animals during recent decades has considerably increased the production (and productivity) of modern food-producing animals at the expense of their robustness, as shown by the degradation of numerous indicators (known as functional traits) such as the efficiency of reproduction, sensitivity to disease, vulnerability to environmental pressure (such as exposure to heat), and

* Corresponding author. INRA, UMR 444 Génétique Cellulaire, F-31326 Castanet-Tolosan, France. Tel: +33 561 285386.
E-mail address: pierre.mormede@toulouse.inra.fr (P. Mormede).

0739-7240/12/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.domaniend.2012.05.002

duration of productive life. At the same time, an increasing awareness toward the negative impact of animal breeding on the environment (such as the production of nitrates, phosphates, and greenhouse gases), an increasing concern of consumers about the deleterious or positive effects of feedstuffs on human health and of citizens about the welfare of farm animals, and the changes in rural lifestyle that result in a reduced workforce have raised new challenges for farm animal production. The necessary increase of production to match the demand of food of animal origin is therefore constrained by new challenges for commercial enterprises involved in the genetic selection of food-producing animals that must be answered to keep and improve their position in an open, highly competitive market. Innovative strategies must be developed urgently to analyze and take into consideration these new characteristics, to be combined with the necessary high level of production and an increasing quality of commercial products, which are prerequisite to the sustainability of animal production.

2. Robustness is the central concept integrating farm animal breeding objectives

The concept of robustness integrates these different breeding goals, as it refers to the combination of a high production potential and a low sensitivity to environmental perturbations [1,2]. For the sustainability of animal breeding, the high production potential must be understood not only in terms of economic profitability but also in terms of minimal environmental impact. In designing the animal of tomorrow, three features should be considered as constituting the core of trait development focus: feed efficiency, adaptability, and product quality.

Increasing feed efficiency is a main avenue to reducing the cost of production (animal feed represents more than 50% to 60% of the total production cost for pig, chickens, milk, and beef) and the environmental burdens caused by animal production systems (reduction of effluents, nitrogen and phosphorus excretion, methane emission). This goal can also be reached using alternative sources of food, such as by-products of agro food and biofuel industries, which would also reduce the competition between animals and humans for noble feedstuff.

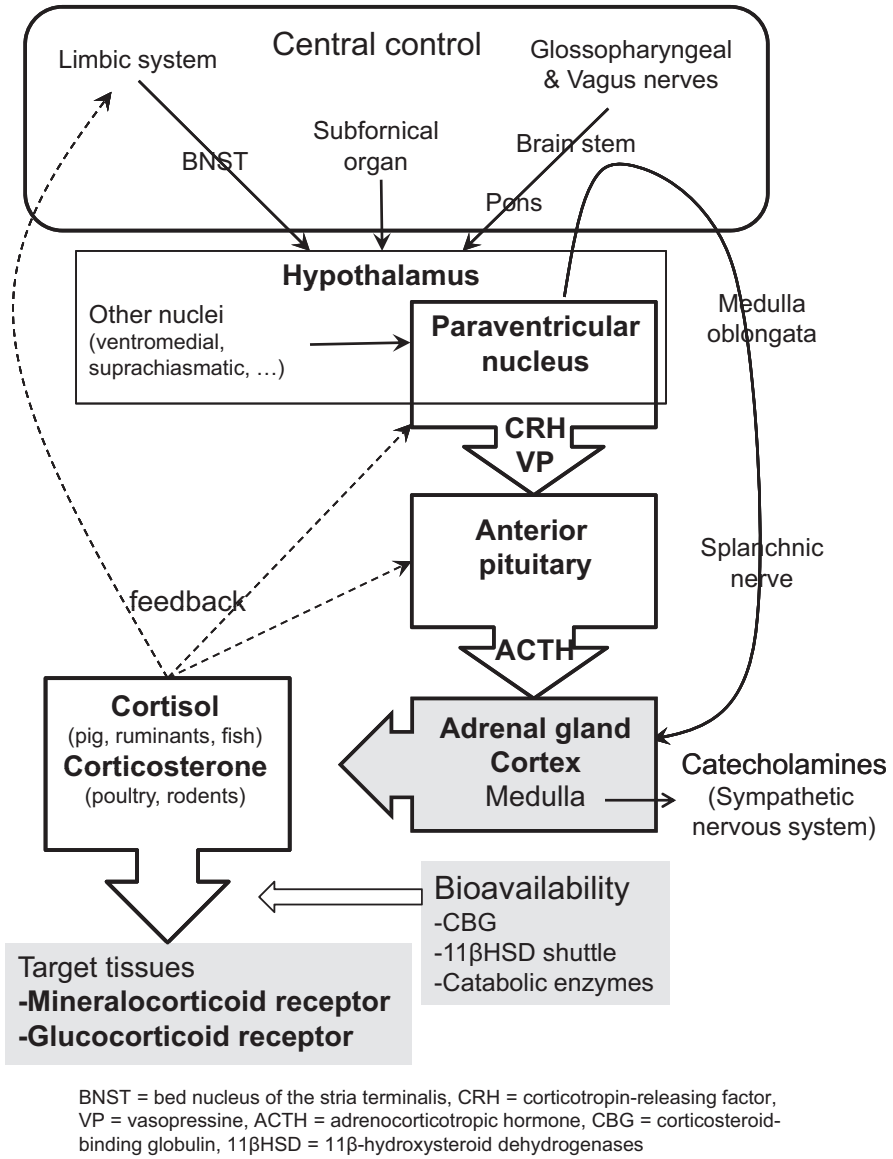
Adaptability is central to animal efficiency. Genetic progress may become constrained in commercial practice if animals are raised under conditions that do not support full expression of their genetic potential because of suboptimal environmental conditions in terms of nutrition, stocking density, temperature, humidity, and pathogen exposure. For instance, pigs raised in commercial environments do not express more than 80% of their genetic potential [3]. Adaptability is a global measure of the sensitivity of the animal to the environment and to the metabolic load of its genetic potential for production traits. Adaptability also includes traits that are sensitive to inadequate environmental conditions, such as disease resistance and mortality in various stages (eg neonatal), altogether known as “functional traits.” Such traits are important not only for performance levels but also for animal health and welfare [4]. Their improvement also has a positive impact on the environment by reducing production losses as well as the need for the preventive and therapeutic use of drugs (such as antibiotics). Finally, changes in rural lifestyle and economic constraints reduce the workforce available for the care of farm animals, which must therefore become more independent.

The quality of animal products is the third category of traits to take into consideration in designing the animals of tomorrow. Food safety is of primary importance for products of animal origin, together with their sensory and technological qualities. However, there is a growing demand for food products that improve consumer health status (eg specific fatty acid composition).

The solution to this multidimensional equation is a major challenge to animal breeding. Numerous avenues are explored to reach these goals and genetics is a major lever in designing the animal of tomorrow. Indeed, all traits cited above and contributing to the sustainability of farm animal production are more or less heritable. However, the challenge is to combine the number and diversity of traits in the selection goals. Genomic selection is a unique opportunity to combine a complex set of traits as long as these traits can be measured accurately in the reference population. Many traits contributing to sustainability are difficult to measure and a considerable effort of detailed and extensive phenotyping will be necessary before it is possible to use this information in genomic selection. In this paper, we present our view that stress neuroendocrine systems, and more specifically the hypothalamic-pituitary-adrenocortical (in short, adrenocortical) axis, are primary contributors to the major phenotypes described above, including stress and adaptation, robustness, zootechnical performances including feed efficiency, and product quality. Furthermore, a considerable genetic variation has been described in adrenocortical axis function that may be used for genetic selection toward the objective of sustainability of farm animal production.

3. Physiology of the adrenocortical axis

The adrenocortical axis [5] and sympathetic nervous system [6] are the primary mediators of the neuroendocrine stress response and, together with behavioral adjustments, contribute to physiological adaptation [7] (Fig. 1). The main output elements of the axis are the glucocorticoid (GC) hormones; cortisol in bovine, pigs, and fish; or corticosterone in birds, synthesized in and released by the adrenal cortex (or suprarenal glands in fish) in response to the adrenocorticotropic hormone (ACTH) released by the anterior pituitary gland under the control of hypothalamic neurohormones corticotrophin-releasing hormone and vasopressin [8,9]. Glucocorticoid hormones are not soluble in water and therefore circulate in blood bound to plasma proteins, such as albumin and the specific carrier corticosteroid-binding globulin (transcortin or CBG). Their liposolubility allows GC hormones to diffuse largely in all tissues and cells, where they act via the glucocorticoid (GR) and mineralocorticoid (MR) nuclear receptors that act as transcription factors, influencing the expression of several hundreds of genes via a wide range of transduction



BNST = bed nucleus of the stria terminalis, CRH = corticotropin-releasing factor, VP = vasopressine, ACTH = adrenocorticotropic hormone, CBG = corticosteroid-binding globulin, 11βHSD = 11β-hydroxysteroid dehydrogenases

Fig. 1. Organization and regulation of the adrenocortical axis. The adrenocortical axis proper is constituted by the hypothalamic (parvicellular part of the paraventricular nucleus)-anterior pituitary (corticotroph cells)-adrenal cortex functional chain releasing glucocorticoid hormones in the general circulation. The hormones act through their receptors on a wide range of tissues. The axis is controlled by central mechanisms and self-regulated by hormonal feedback. The main sources of genetic variation are shown on a gray background: sensitivity of the adrenal gland to ACTH, which is also under sympathetic control by the splanchnic nerve, hormone bioavailability (including transport mechanisms and catabolic processes), and functional efficiency of receptor transduction mechanisms (see text for details).

mechanisms [10–13]. They influence numerous metabolic pathways, the immune system, inflammatory processes, and brain functions, to mention the most important. They also exert strong feedback on the axis [14]. Glucocorticoid hormones are metabolized in the liver by oxydoreduction reactions and then conjugated (sulfo- and glucuronoconjugates that are eliminated in urine as 17 hydroxysteroids and a small fraction of untransformed steroids that can be measured as an index of their production). The 11β-hydroxysteroid dehydrogenase (11β-HSD) shuttle plays an important role in regulating glucocorticoid hormone availability. The type 1 enzyme (11β-HSD1) allows the regeneration of cortisol (or corticosterone) from inert cortisone (or 11-dehydrocorticosterone) and is present in various tissues of the body—including the liver, adipocytes, bones, and brain—acting as an intracellular glucocorticoid amplifier. It is also involved in the regulation of the axis. The type 2 enzyme (11β-HSD2) has a localization restricted to mineralocorticoid responsive tissues and the fetoplacental unit; it allows the reverse reaction, metabolizing glucocorticoids to inert compounds, and therefore protects access to the MR by glucocorticoid hormones [15].

The activity of the adrenocortical axis is highly variable because of the combination of numerous influences on secretory activity and pharmacokinetic properties. The secretion of ACTH and cortisol is pulsatile in most species, with a pulse frequency of about 90 min, follows a diurnal cycle and is influenced by meals, physical activity, and environmental conditions (see [16] for a review and species-specific features). Furthermore, short half-lives of distribution and elimination of cortisol (for example $<$ 2 min and 20 min, respectively, in sheep [17] and 3.5 min and 36.5 min, respectively, in pigs [Mormede and Galtier, unpublished data]) allow a rapid adaptation of circulating levels to physiological needs. However, accurate measurement of the activity of the axis is challenging [16].

The effects of GC hormones on energy metabolism, in concert with insulin, are central to their role in adaptation [18–20]. They induce protein and lipid catabolism in peripheral tissues (eg muscle, skin, and thymus), releasing amino acids, glycerol, and free fatty acids that are used in the liver for anabolism, including new protein synthesis and gluconeogenesis [21]. Glucocorticoid hormones have also an anti-insulin effect. Altogether these processes increase the availability of energetic metabolites for behavioral adjustments (the "fight-or-flight response") and metabolic adaptation (eg thermoregulation). However, when the mobilized energy is not consumed and in the presence of insulin, metabolites are taken up by adipose tissue, promoting the synthesis of lipids. The result is an increase of energy storage (fat and glycogen) at the expense of tissue proteins. It has been shown in rats that the lipid: protein ratio of the carcass, measured 2 wk after adrenalectomy and subcutaneous implantation of a corticosterone pellet, is directly proportional to the dose of corticosterone [22]. In the same experiment, Devenport and colleagues showed that the final body weight and feed efficiency followed a bell-shape curve with increasing dosages of corticosterone. Several mechanisms are involved in these effects. At the lowest doses, feed intake is reduced because corticosterone plays an important role in the regulation of feeding behavior [23,24]. Under normal physiological conditions, the MR is tonically activated by low basal levels of circulating corticosterone. The activation of MR is required for the maintenance of fat ingestion and fat deposition that occurs during most meals of the feeding cycle. In contrast, the GR is phasically activated by moderate levels of corticosterone normally reached during the circadian peak or during periods of increased energy requirements, such as after exercise and food restriction or during stress, when corticosterone levels increase further. Activation of this receptor is required for the natural surge in carbohydrate ingestion and metabolism that is essential at the onset of the active feeding cycle when the body's glycogen stores are at their nadir, and gluconeogenesis is needed to maintain blood glucose levels or to provide additional substrates for glucose when necessary [23]. Reduced feed efficiency at the lowest corticosterone levels may also result from an excessive sympathetic tone, with catabolic effects, that is negatively regulated by GC [25,26]. At higher dosages of corticosterone, the direct effects of GC via GR described above (peripheral catabolism and promotion of energy storage) are responsible for the lower than optimal feed efficiency and body weight gain. These metabolic effects of GC are not favorable to animal production when growth rate, feed efficiency, and lean carcasses are the main selection objectives; however, they may positively influence adaptation and functional traits.

Glucocorticoid hormones have an important effect on the immune system. Indeed, the decrease in thymus size is a historical symptom of the stress syndrome as initially described by Hans Selye [5] and is a perfect bioassay of glucocorticoid levels [27,28]. Glucocorticoid hormones and their synthetic analogs are still the most potent anti-inflammatory drugs for clinical use.

Cortisol and stress also influence the specific immune response in a complex manner [29,30]. Conversely, acute inflammation is a powerful trigger of the adrenocortical axis, as shown, for instance, under experimental conditions by the response to bacterial lipopolysaccharide [31,32]. In chronic inflammation however, the cortisol-inflammation relationships become more complicated. Glucocorticoid resistance develops and activation of the adrenocortical axis, which may appear as an adaptive program positively selected for short-lived inflammatory responses (energy appeal reaction), becomes a disease-inherent pathogenetic factor, if it continues too long, that can drive systemic disease sequelae of chronic inflammatory diseases such as metabolic syndrome [33].

4. Genetics of adrenocortical axis activity and function

Individual variations of adrenocortical axis activity are well documented, and the reproducibility of the tests for adrenocortical axis function discloses stable individual characteristics [34–38].

The influence of genetic factors has been suggested by twin and family studies in humans [39–49] and pigs [50]. Large variations have been described between inbred strains of mice [51–53] and rats [54–61] and between farm animal breeds [62–72]. A few contrasted lines or breeds have played an important role in the study of the molecular bases of genetic variation in stress responses. In rats, most research has been done with Lewis, Fischer 344, Brown Norway, and Wistar Kyoto inbred strains and their intercross [73–79]. In mice the C57BL/6 and DBA/2 inbred strains are contrasted for almost all characteristics of the adrenocortical axis [53,80–81] and the BXD panel of recombinant inbred strains derived from these 2 parental strains is a powerful tool for an integrated study of the molecular bases of these differences (eg [82] and http://www.genenetwork.org). In pigs, the Meishan (MS) Chinese breed has been frequently compared with and bred with European White-type breeds. Meishan pigs give birth to larger and more lively litters [83–86] and have a lower growth rate and feed efficiency, as well as fattier carcasses with lower muscle content and a better meat quality index [87,88]. As with adrenocortical axis activity, circulating levels of cortisol are much higher, close to the values measured in wild boars [66,89–91]. These high levels result not only from a higher production of hormones, as can be measured in urine [68,92], but also from higher circulating levels of CBG [93–95]. The higher production of cortisol is at least partly the result of a higher susceptibility of the adrenal cortex to ACTH [67,96]. Exploration of corticosteroid receptor properties showed higher densities of hippocampal MR in MS pigs and of pituitary GR in Large White (LW) pigs [97]. The difference in the MR/GR balance in the hippocampus and pituitary could be involved in the different adrenocortical axis activity between the 2 breeds [98–100]. These breeds have been largely used to search for loci involved in genetic variation of production traits, as well as behavioral and neuroendocrine stress responses [101].

Finally, it has been shown in a wide range of animal species that adrenocortical axis activity is responsive to genetic selection: confinement stress in trout [72,102,103], adrenal response to ACTH [104] and social stress [105] in chickens, cold stress in turkeys [106], immobilization stress in Japanese quail [107] and mice [108], and suspension test in ducks [109]. The response to selection is usually strong, with realized heritability between 0.4 and 0.5, showing that genetics is a powerful tool to tune adrenocortical axis activity in the desired direction.

5. Sources of genetic variation in adrenocortical axis activity and functional consequences

5.1. Sensitivity of the adrenal gland to ACTH

All components of the adrenocortical axis and its regulatory inputs may contribute to genetic variation (Fig. 1). The best documented process is the sensitivity of the adrenal gland to ACTH, which tunes the production of GC hormones. It has been shown in humans [35,36] and in pigs [37] that this response is an individual trait ("the corticotroph phenotype" [35]) and we have calculated in a family study with LW pigs a heritability of 0.51 [50]. Divergent lines of turkey could be selected on the basis of their response to ACTH injection, with a realized heritability of 0.28 [106]. In both trout [110] and duck [109], the adrenal response to ACTH appears to be a major component of the differences between lines divergently selected for the adrenocortical axis response to confinement and suspension stress, respectively. Differential gene expression studies in pigs [96,111–113] and chickens [114] have produced a list of candidate genes related to differences in sensitivity to ACTH. The relationship between adrenal sensitivity to ACTH and production traits is well documented. In a large population study in pigs, Hennessy and Jackson showed that animals with higher sensitivity to ACTH (as measured at 3 wk) were lighter, with a slower growth curve and a lower feed efficiency

[115]. In rams, residual feed intake was shown to be directly proportional to the release of cortisol after injection of ACTH [116]. The same tendency was found in Brahman steers, with a significant correlation with the marbling score of meat [117]. However, we did not find any difference in adrenocortical axis activity between 2 lines of LW pigs genetically selected for divergent feed efficiency ([118] and unpublished results), showing that these 2 functions may be independently influenced by genetic factors.

5.2. Hormone bioavailability

Hormone bioavailability is another important mechanism of genetic variation. Little information is available in farm animals on the metabolic disposal of GC hormones and its genetic variation, despite their importance in the regulation of GC hormone activity [119]. In contrast, the influence of CBG has been raised by the discovery of the linkage between circulating cortisol levels (basal and poststress) and a genetic locus including the CBG gene (SERPINA6) in an F2 intercross between MS and LW pigs, explaining 20% of the variance of the F2 population [101]. The same region was also found to be linked, although more weakly, to several parameters of body composition, findings consistent with an increased adrenocortical axis function. The association with CBG was confirmed using CBG levels instead of cortisol, and in this study we confirmed in some F2 families that the CBG gene could be a regulator of fat accumulation and muscle content in the carcass, suggesting that specific haplotypes are involved in this association [95]. Indeed, numerous polymorphisms (SNP for single nucleotide polymorphism) were detected, both between and within breeds, 4 of which lead to amino acid substitution. The in vitro and in vivo analysis revealed that at least 1 of these polymorphisms could influence CBG binding of cortisol or CBG mRNA expression [94]. We have also explored the relationships between CBG levels and various measures (carcass composition and meat quality) in 5 different breeds with inconsistent results [120]. Only 2 genetic stocks (pure LW and an LW by MS advanced intercross line) showed correlations between CBG levels and circulating cortisol levels and production traits. Furthermore, the nature and the direction of correlations differed in the 2 lines. Indeed, in humans as well, complex relationships were found among CBG genotypes, adrenocortical axis phenotypes, and obesity [121,122]. It is interesting to note here that even when plasma cortisol levels are correlated with plasma CBG, urinary levels of cortisol are always independent of CBG levels and therefore give a more accurate evaluation of cortisol production than circulating levels, as shown in humans [123,124]. The same locus was found to influence the adrenocortical axis response to stress in rats [125] and several phenotypes that may be influenced by adrenocortical axis activity (see review in [126]). The role of CBG in the regulation of adrenocortical axis activity and related traits was studied in knockout mouse models, showing that this carrier protein may play an important role in GC hormone activity, particularly in response to stress [127,128]. At this stage, we need more information about the physiological role of CBG that has always been balanced between the "free hormone hypothesis," stating that only the unbound hormone is available for transfer into the target cells, and the "reservoir hypothesis," stating that CBG sequestrates glucocorticoids in plasma and is therefore able to release large amounts of hormone in the tissues [129,130]. The influence of genetic polymorphisms on these processes and the final physiological effects of GC hormones should be explored further.

5.3. Receptor function and transduction mechanisms

Genetic variability at the level of corticosteroid receptors is well documented in humans, as is its contribution to a large range of pathologic conditions [13,131–133]. We showed in rats that the adipogenic effects of CG hormones vary considerably across strains as a consequence of different functional activity of their receptors [134,135]. In contrast, little information is available in farm animal species. Binding properties of MR and GR have been studied in LW and MS pigs [97], and an SNP of the NR3C1 gene was shown to influence circulating cortisol levels and adrenal gland weight [136], but little is known about the efficiency of the different transduction pathways involved in corticosteroid hormone function. It may be anticipated that genetic polymorphisms in specific pathways would be a powerful lever to potentate the favorable effects of these hormones and downregulate their undesirable consequences. This should be an important line of research for the future.

5.4. Higher control mechanisms

Finally, higher levels of control of the adrenocortical axis (pituitary, hypothalamic, and suprahypothalamic) are difficult to explore directly in farm animals. A promising approach consists of the search of molecular polymorphisms in the genes encoding constitutive or regulating proteins of the adrenocortical axis and its regulatory nervous pathways [8]. Murani and colleagues found multiple

and consistent associations with SNP in NR3C1 and AVPR1B (a receptor for vasopressin that interacts with corticotrophin-releasing hormone to release ACTH from the pituitary), providing convincing evidence for genuine effects of their DNA sequence variation on stress responsiveness and aggressive behavior [136]. Terenina and colleagues (unpublished observations) extended these findings to the monoaminergic neural pathways regulating adrenocortical axis activity.

5.5. System genetics

A major point to consider here is how these different sources of genetic variation in the adrenocortical axis, its receptor and postreceptor transduction mechanisms, and its regulatory pathways contribute to the final function(s) of corticosteroid hormones. The adrenocortical axis is strongly regulated by various feedback mechanisms involving the effects of corticosteroid hormones on different components of the axis and higher regulating pathways such as the hippocampus, via the classical MR and GR, as well as membrane receptors [98,137,138]. Consequently, it is expected that any mutation at one level of the system will reorganize the whole axis so that the functional consequence of the initial change may be dampened or amplified, depending on the plasticity of the other components. Indeed, several sources of genetic variability are usually found in the same model [60,61,74], but little is known about the interactions among various sources of variability within the axis and how they eventually compensate for or potentiate each other. In this context, it is important to question the functional significance of various parameters classically used to evaluate adrenocortical axis activity. For instance, when comparing the response of 3 mouse strains to various stressors, the strain with the largest response of plasma corticosterone displayed the lowest biological response as measured by the increase of glucose or decrease of interleukin 6 plasma levels [80,81]. These results clearly show that plasma concentration of GC hormones, the gold standard to measure the intensity of adrenocortical axis activity and response to stress, is not necessarily a reliable index of the adrenocortical axis functional tone. For a complete characterization of the genetic variation in adrenocortical axis activity and its consequences on robustness traits, we need a more exhaustive evaluation of the different components of the axis, such as the urinary concentration of GC hormones and metabolites that reflect the production rate and metabolism, the salivary concentration proportional to the free circulating hormone, CBG levels, and, perhaps more importantly, robust measures of functional activity. Indeed, GC hormone excretion in urine is suited to studying individual differences in adrenocortical axis activity because it is not influenced by CBG concentration, unlike plasma concentration [93], nor by rapid (frequently pulsatile) changes in hormone secretion (urine accumulates over several hours), nor by sample handling (urine collection is a noninvasive method). Finally, urine collection allows the measurement of catecholamine excretion as an index of the sympathetic nervous system activity [16,139]. Several studies have shown a relationship between GC hormone levels in urine and carcass composition, as well as catecholamine levels and meat quality [92,140–143]. Little information is available with regard to the functional output of the system. The use of functional genomics has been recently promoted by Cole [144] to study stress and coping in humans. This approach is based on a genome-wide transcriptional profiling of circulating blood cells associated with bioinformatic analysis of the balance between GR- and nuclear factor κB-regulated genes in the differentially expressed transcripts, with these 2 systems—cortisol transduction and inflammatory responses—opposing each other. The activation of the sympathetic nervous system can also be analyzed through the expression of genes regulated by CREB/ATF transcription factors [144,145]. On one hand, the autonomic nervous system plays a specific role in metabolic regulation and stress responses [6]. It has also been shown to have specific genetic variation (see [146] for review). On the other hand, the adrenocortical axis and sympathetic nervous system have strong relationships. We have shown, for instance, that cortisol and adrenaline levels measure in urine collected after slaughter in a genetically mixed population of pigs were highly correlated with each other, much more so than cortisol and noradrenaline levels [140,143]. One mechanism to explain this relationship is the regulation by cortisol of the enzyme PNMT, which catalyzes the methylation of noradrenaline into adrenaline [147]. It is also possible that the adrenal cortex (cortisol) and medulla (adrenaline) are somehow coactivated, but that the adrenocortical axis (cortisol) and the sympathetic nervous system (noradrenaline) are largely independent. Further experiments should sort out the respective influence of these mechanisms.

6. Adrenocortical axis contribution to adaptation-related traits

As mentioned previously, adaptability is a global measure of the sensitivity of the animal to the environ-

ment and to the metabolic load of its genetic potential for production traits. Adaptability also includes traits that are sensitive to inadequate environmental conditions, such as disease resistance and mortality in various stages (eg neonatal) or leg soundness, altogether known as "functional traits." Such traits are important not only for performance levels but also for animal health and welfare.

A few examples are available to demonstrate the positive influence of the adrenocortical axis on several functional traits. The adrenocortical axis is essential for regulating intrauterine fetal homeostasis, controlling the normal timing of parturition, and ensuring timely differentiation and maturation of vital organ systems for postpartum survival. These effects are mediated by a surge of cortisol production and CBG synthesis in late gestation (eg [148–155]). In perinatal piglets, for instance, carbohydrate metabolism is described as being closely related to piglet survival. Prenatal glycogen deposition, glucose homeostasis, and thermoregulation are important factors for maturity [156], and cortisol is a key hormonal factor in increasing glycogen synthesis [157]. The low level of cortisol in neonatal calves may also be responsible for the lower endogenous production of glucose in preterm calves [158]. Heart glycogen is important for resistance against anoxia during delivery. Liver glycogen maintains glucose homeostasis during parturition and the immediate postpartum period. Muscle glycogen stores have a function first in postnatal thermogenesis, especially before colostrum intake, and later if energy intake is inadequate. Availability of glycogen stores is critical in the absence of brown adipose tissue for temperature regulation in neonatal animals [159,160]. In their search for biological traits in piglets related to their own genetic merit for survival, Leenhouwers and colleagues [161,162] found that the only biological characteristics correlated (positively) with the estimated breeding value for piglet survival were the size of the adrenal glands and the concentration of cortisol in cord blood collected at birth. These endocrine measurements were also correlated positively with the relative weight of the small intestine and higher concentrations of glycogen in the liver and muscle that reflect the gluconeogenic properties of cortisol [155,163] and its influence on intestinal maturation [164,165]. The high level of adrenocortical axis activity in MS pigs may at least partly explain the exceptional viability of their piglets [84], although data are still incomplete on the evaluation of adrenocortical axis activity in fetuses from different breeds [166].

Experimental data also show that adrenocortical axis activity may contribute to heat resistance. Michel and collaborators studied individual variations in responses to heat stress in rats [167]. The animals with the strongest adrenocortical axis response, as measured by the circulating corticosterone levels, displayed a more efficient physiological adaptation to the heat stimulus, with a lower increase of core temperature and hemoconcentration and a reduced inflammatory response in the brain. These differences reflect the physiological effects of glucocorticoid hormones [168] and show that the animals that mount a strong stress response adapt better to the stressor. Similar results were obtained in chickens. Animals from the Red Jungle fowl or the indigenous village fowl genotypes, with high or medium basal levels of plasma corticosterone, respectively, did not show any response to acute heat exposure (36°C, 3 h, as measured by deep body temperature, expression of heat shock protein 70 in the brain, plasma corticosterone concentration, and blood heterophil:lymphocyte ratio). On the contrary, chickens from a selected line (Cobb 500) with low basal concentrations of corticosterone showed a marked response [169].

Finally, experimental evidence in poultry shows that genetic selection for the intensity of the adrenocortical axis stress response has a complex influence on immune responses and resistance to diseases. For instance, chickens from a line selected for high levels of plasma corticosterone when housed in an environment facilitating considerable social interaction were more resistant to parasitic infestation by *Eimeria necatrix* than those from a line selected for low levels of plasma corticosterone housed in an environment that minimized social interaction [170]. Recently, Minozzi and colleagues showed that genetic selection of Leghorn chickens for different immune traits did not modify corticosterone response to stress or to ACTH, but within lines, several endocrine traits correlated with the level of immune parameters. It is worth noting, for instance, that in the line selected for high antibody response to Newcastle disease virus, vaccine basal corticosterone concentrations were negatively correlated to phagocytic activity measured by carbon clearance, but stress corticosterone response was positively correlated with the antibody response [171]. These differences reflect the complex effects of corticosteroid hormones on the immune system and inflammatory processes [29,30].

7. Adrenocortical axis and selection for robustness

As explained earlier, the concept of robustness integrates diverse components that frequently appear to be

contradictory. Indeed, local breeds of minimally selected animals are usually well adapted to their (eventually harsh) environment, but their absolute production level is frequently low compared with selected genotypes. Conversely, genetically selected, highly productive stocks frequently show signs of reduced robustness [4,172–175]. Reduced robustness may be associated with increased pain and reduced animal welfare, caused, for example, by increased lameness and susceptibility to other diseases, reduced survival of newborns, and lower functional longevity. The trade-off between productivity and robustness is predicted by the resource allocation theory [176,177]: the energetic resources of an individual are limited and their allocation across metabolic functions is optimized toward the best adaptation of the individual to its environment (ie fitness). Genetic selection for production traits logically redirects resources toward these production traits, at the expense of other traits (such as functional traits). When resources are not sufficient to support full expression of the production potential, the interaction between the selected genotype and a restrictive environment may reduce the resilience of the animal. Genetic selection for robust animals must balance these different components. It must be noted here that the genetic gain from intense selection on production traits is only partly maintained at the level of commercial production because of the suboptimal level of environmental conditions [3], leaving some space for a small reduction in absolute production potential as long as a significant gain is obtained in resilience to environmental negative factors.

Several breeding strategies can be implemented to increase robustness [2]. First, genetic improvement in functional traits, such as leg soundness, mortality rates at various stages of the animal's life, and functional longevity, is possible when these traits are properly included in breeding goals and selection criteria. This goal is already implemented in existing breeding programs (eg [178]). Although valuable, this approach requires extensive and time-consuming phenotyping of the animals for multiple and frequently difficult-to-measure traits. Current efforts toward the discovery of molecular bases for genetic variation of these complex traits will likely nominate DNA polymorphisms to be used for genomic selection. Second, the global sensitivity to the environment can also be measured by techniques such as the reaction norm analysis that compares animals with identical genotypes across different environments. This is a difficult endeavor and heritability of the character is often low [179]. Sensitivity to the environment may also contribute to the environmental variance of a trait, which has been shown to be under genetic control. The reduction of trait variance by genetic selection is also known as canalizing selection, or canalization [180]. To date, this approach has not yielded practical solutions for genetic selection. The third strategy, which is the topic of the present review, focuses on the molecular genetics of neuroendocrine stress responses, more specifically the adrenocortical axis.

The adrenocortical axis has a central role in the regulation of the genetic trade-off mechanisms between production and adaptation. Genetic selection for domesticated phenotypes usually reduces the activity of the adrenocortical axis, as shown, for instance, in pigs [90], chickens [169], sheep [181–184], guinea pigs [185], silver foxes [186], or rats [187]. This downregulation of stress responses may be considered an adaptation to living in a biologically safe, predator-free environment that is favorable to improve production traits mostly based on protein anabolism (the Darwinian concept of stress [188]). However, intense selection for production traits has further driven down the activity of the adrenocortical axis, as we showed in the LW breed of pigs by comparing progeny from sires born in 1977 (frozen semen) vs 1998–2000 [189]. This trend results from the above-mentioned negative effect of cortisol on production traits and carcass composition, so that adrenocortical axis activity was counterselected in the selection process. As a consequence, this decrease in adrenocortical axis activity may explain part of the compromised robustness that coincides with overfocused genetic improvement of production traits in farm animals (Fig. 2).

We have shown that genetic variation can be found at every step of the adrenocortical axis function [133]. Genetic polymorphisms could therefore be used in marker-assisted or genomic selection to increase robustness by improving functional traits without compromising the high level of production. This objective does not appear to be out of reach. Indeed, the functional variability of the adrenocortical axis is usually large, even in genetically homogeneous populations. A 30-fold range of urine cortisol concentrations was found in each of 5 pig lines, much more than the variation of production traits (Fig. 3) [92]. In the abovementioned study of genetic trends of stress-responsive systems in the French LW, we found a −0.27 correlation between cortisol levels (in urine collected from the bladder after slaughter) and carcass lean content, so that only $(0.27)^2 = 7.3\%$ of the variance of leanness is related to differences in cortisol production [189]. It is

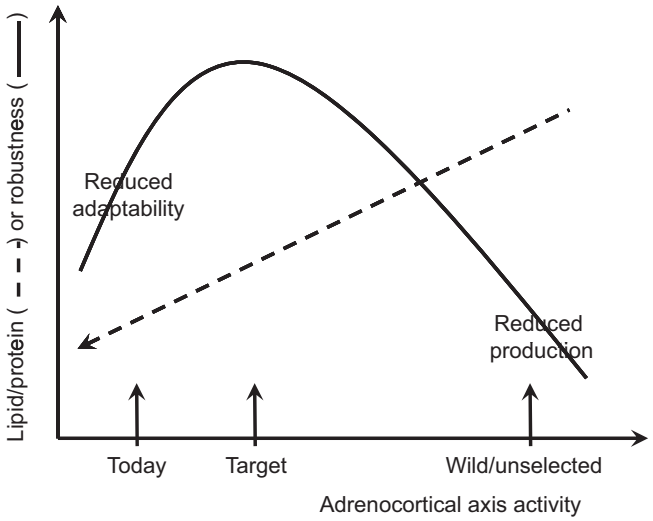


Fig. 2. Schematic representation of the relationships between adrenocortical axis activity and robustness. High levels of adrenocortical axis activity as measured, for instance, in wild or unselected populations are usually associated with low levels of production. Intense selection for rapid growth and lean carcasses has concomitantly reduced the activity of the adrenocortical axis (dashed line). We hypothesize that this low level of activity contributes to the reduced adaptability of modern, highly selected genotypes. Genetic selection for a more active adrenocortical axis could improve the balance between production and adaptability (defined here as robustness).

therefore possible to envisage the selection for a stronger adrenocortical axis to improve robustness without compromising production traits. Indeed, it was previously shown that the introduction of functional traits in selection programs could efficiently improve robustness without compromising the genetic gain on production traits [178]. On the other hand, even if the maximal genetic potential of the animals is slightly reduced, the gain can be obtained via a better realization of this potential under commercial conditions (Fig. 2).

Furthermore, we should be able to finely tune this genetic approach by sorting the polymorphisms according to their functional outcome. Considering the complexity of the physiological effects of glucocorticoid hormones that up- or downregulate hundreds of genes, it would not be surprising that specific gene polymorphisms would more specifically improve functional traits (and should therefore be positively selected), whereas others would be more deleterious on production traits (and should therefore be negatively selected). However, we have no overall view integrating these diverse sources of genetic variability within the system and their functional consequences on the different components of robustness. System genetics and modeling approach should deliver the necessary knowledge to solve this challenge of selecting more robust animals in the context of strong economic pressure.

8. Conclusion

The adrenocortical axis plays a central role in the physiology of food-producing animals as a trade-off mechanism between production and functional traits that are directly related to adaptation of the animal to environmental constraints. These functional traits have

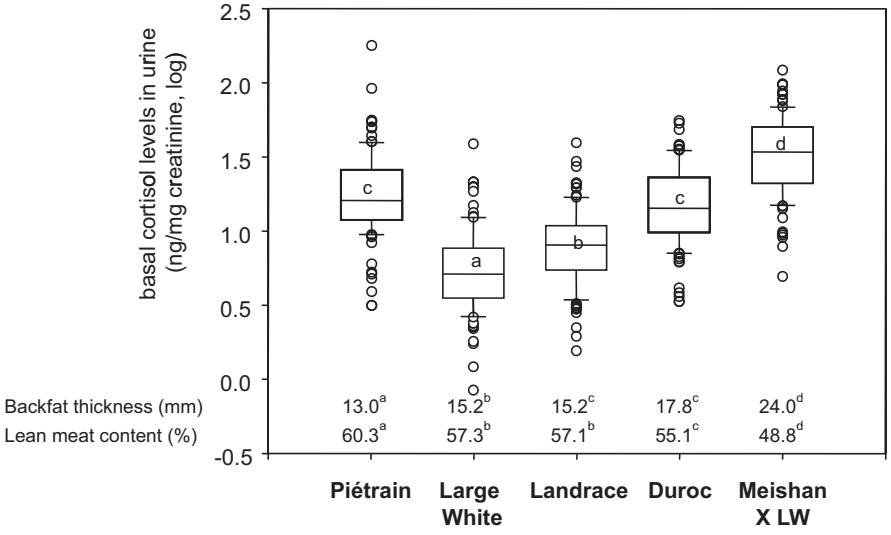


Fig. 3. Cortisol production and fatness in pigs. Box-plot representation of cortisol concentrations measured in urine of resting female pigs from 5 genetic stocks (100 pigs per stock) differing in their level of adiposity (back-fat thickness and estimated lean meat content). Columns with different letters differ significantly ($P < 0.05$). Except for the Piétrain stock, higher urinary cortisol levels are associated with higher fatness. Note the large distribution of cortisol levels within a breed, with a range of approximately 1.5 log units (300-fold). Data are from [92].

suffered from several decades of intense selection overfocused to production traits and at the same time have gained importance in breeding objectives because of new challenges such as the environmental impact of farm animal production, animal welfare, and the changes in rural lifestyle resulting in a reduced workforce. Increasing animal robustness will be obtained by improving the functional traits and at the same time maintaining as much of the high production potential as possible. Strong genetic factors influence adrenocortical axis activity and function, so it is conceivable to increase robustness by selecting animals with higher adrenocortical axis activity. A more detailed analysis of the molecular bases of genetic variability should allow the development of a fine-tuned strategy for genomic selection of the alleles maximizing the gain on functional traits while minimizing the impact on production.

References

[1] Knap PW. Breeding robust pigs. Aust J Exp Agric 2005;45: 763–73.

[2] Mormède P, Foury A, Terenina E, Knap PW. Breeding for robustness: the role of cortisol. Animal 2011;5:651–7.

[3] Schinckel AP. Modeling, management and selection of genetics for optimal commercial performance. In: *German Society for Animal Science*. Giessen, Germany: 9th World Congress on Genetics Applied to Livestock Production; 2010: paper 0045.

[4] Knap PW. Robustness, In: Rauw WM, editor. *Resource Allocation Theory Applied to Farm Animal Production*. Wallingford, UK: CABI; 2009:288–301.

[5] Selye H. A syndrome produced by diverse nocuous agents. Nature 1936;138:32–3.

[6] Cannon WB. Stresses and strains of homeostasis. Am J Med Sci 1935;189:1–14.

[7] Dantzer R, Mormède P. Stress in farm animals: a need for reevaluation. J Anim Sci 1983;57:6–18.

[8] Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 2009;10: 397–409.

[9] Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009;5:374–81.

[10] Nicolaides NC, Galata Z, Kino T, Chrousos GP, Charmandari E. The human glucocorticoid receptor: molecular basis of biologic function. Steroids 2010;75:1–12.

[11] Necela BM, Cidlowski JA. Mechanisms of glucocorticoid receptor action in noninflammatory and inflammatory cells. Proc Am Thorac Soc 2004;1:239–46.

[12] Gross KL, Lu NZ, Cidlowski JA. Molecular mechanisms regulating glucocorticoid sensitivity and resistance. Mol Cell Endocrinol 2009;300:7–16.

[13] Pascual-Le Tallec L, Lombès M. The mineralocorticoid receptor: a journey exploring its diversity and specificity of action. Mol Endocrinol 2005;19:2211–21.

[14] Dallman MF, Akana SF, Cascio CS, Darlington DN, Jacobson L, Levin N. Regulation of ACTH secretion: variations on a theme of B. Recent Prog Horm Res 1987;43:113–73.

[15] Seckl JR. 11beta-hydroxysteroid dehydrogenases: changing glucocorticoid action. Curr Opin Pharmacol 2004;4:597–602.

[16] Mormède P, Andanson S, Aupérin B, et al. Exploration of the hypothalamic-pituitary-adrenal function as a tool to evaluate animal welfare. Physiol Behav 2007;92:317–39.

[17] Paterson JYF, Harrison FA. The specific activity of plasma cortisol in sheep after intravenous infusion of [1,2-3H2]cortisol, and its relation to the distribution of cortisol. J Endocrinol 1968;40:37–47.

[18] Akana SF, Strack AM, Hanson ES, Dallman MF. Regulation of activity in the hypothalamo-pituitary-adrenal axis is integral to a larger hypothalamic system that determines caloric flow. Endocrinology 1994;135:1125–34.

[19] Dallman MF, Strack AM, Akana SF, et al. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front Neuroendocrinol 1993;14:303–47.

[20] Strack AM, Sebastian RJ, Schwartz MW, Dallman MF. Glucocorticoids and insulin: reciprocal signals for energy balance. Am J Physiol 1995;268:R142–9.

[21] Thaxton JP, Puvadolpirod S. Model of physiological stress in chickens 5. Quantitative evaluation. Poult Sci 2000;79:391–5.

[22] Devenport L, Knehans A, Sundstrom A, Thomas T. Corticosterone's dual metabolic actions. Life Sci 1989;45:1389–96.

[23] Tempel DL, Leibowitz SF. Adrenal steroid receptors: interactions with brain neuropeptide systems in relation to nutrient intake and metabolism. J Neuroendocrinol 1994;6:479–501.

[24] Devenport L, Knehans A, Thomas T, Sundstrom A. Macronutrient intake and utilization by rats: interactions with type I adrenocorticoid receptor stimulation. Am J Physiol 1991;260: R73–81.

[25] Kvetnanský R, Fukuhara K, Pacák K, Cizza G, Goldstein DS, Kopin IJ. Endogenous glucocorticoids restrain catecholamine synthesis and release at rest and during immobilization stress in rats. Endocrinology 1993;133:1411–9.

[26] Dailey JW, Westfall TC. Effects of adrenalectomy and adrenal steroids on norepinephrine synthesis and monoamine oxidase activity. Eur J Pharmacol 1978;48:383–91.

[27] Cador M, Dulluc J, Mormède P. Modulation of the locomotor response to amphetamine by corticosterone. Neuroscience 1993;56:981–8.

[28] Levin N, Akana SF, Jacobson L, Kuhn RW, Siiteri PK, Dallman MF. Plasma adrenocorticotropin is more sensitive than transcortin production or thymus weight to inhibition by corticosterone in rats. Endocrinology 1987;121:1104–10.

[29] Salak-Johnson JL, McGlone JJ. Making sense of apparently conflicting data: stress and immunity in swine and cattle. J Anim Sci 2007;85:E81–8.

[30] Webster Marketon JIW, Glaser R. Stress hormones and immune function. Cell Immunol 2008;252:16–26.

[31] Williams PN, Collier CT, Carroll JA, Welsh TH, Laurenz JC. Temporal pattern and effect of sex on lipopolysaccharide-induced stress hormone and cytokine response in pigs. Domest Anim Endocrinol 2009;37:139–47.

[32] Carroll JA, Burdick NC, Reuter RR, et al. Differential acute phase immune responses by Angus and Romosinuano steers following an endotoxin challenge. Domest Anim Endocrinol 2011;41:163–73.

[33] Straub RH, Buttgereit F, Cutolo M. Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases—a role for misguided energy regulation. Clin Exp Rheumatol 2011;29:S23–31.

[34] Tanaka K, Shimizu N, Imura H, et al. Human corticotropin-releasing hormone (hCRH) test: sex and age differences in plasma ACTH and cortisol responses and their reproducibility in healthy adults. Endocr J 1993;40:571–9.
[35] Bertagna X, Coste J, Raux-Demay MC, Letrait M, Strauch G. The combined corticotropin-releasing hormone/lysine vasopressin test discloses a corticotroph phenotype. J Clin Endocrinol Metab 1994;79:390–4.
[36] Coste J, Strauch G, Letrait M, Bertagna X. Reliability of hormonal levels for assessing the hypothalamic-pituitary-adrenocortical system in clinical pharmacology. Br J Clin Pharmacol 1994;38:474–9.
[37] Hennessy DP, Stelmasiak T, Johnston NE, Jackson PN, Outch KH. Consistent capacity for adrenocortical response to ACTH administration in pigs. Am J Vet Res 1988;49:1276–83.
[38] Huizenga NA, Koper JW, De Lange P, et al. Interperson variability but intraperson stability of baseline plasma cortisol concentrations, and its relation to feedback sensitivity of the hypothalamo-pituitary-adrenal axis to a low dose of dexamethasone in elderly individuals. J Clin Endocrinol Metab 1998; 83:47–54.
[39] Meikle AW, Stringham JD, Woodward MG, Bishop DT. Heritability of variation of plasma cortisol levels. Metabolism 1988;37:514–7.
[40] Kirschbaum C, Wüst S, Faig HG, Hellhammer DH. Heritability of cortisol responses to human corticotropin-releasing hormone, ergometry, and psychological stress in humans. J Clin Endocrinol Metab 1992;75:1526–30.
[41] Linkowski P, van Onderbergen A, Kerkhofs M, Bosson D, Mendlewicz J, van Cauter E. Twin study of the 24-h cortisol profile: evidence for genetic control of the human circadian clock. Am J Physiol 1993;264:E173–81.
[42] Inglis GC, Ingram MC, Holloway CD, et al. Familial pattern of corticosteroids and their metabolism in adult human subjects—the Scottish adult twin study. J Clin Endocrinol Metab 1999;84:4132–7.
[43] Franz CE, York TP, Eaves LJ, et al. Genetic and environmental influences on cortisol regulation across days and contexts in middle-aged men. Behav Genet 2010;40:467–79.
[44] Steptoe A, van Jaarsveld CHM, Semmler C, Plomin R, Wardle J. Heritability of daytime cortisol levels and cortisol reactivity in children. Psychoneuroendocrinology 2009;34:273–80.
[45] Schreiber JE, Shirtcliff E, Van Hulle C, et al. Environmental influences on family similarity in afternoon cortisol levels: twin and parent-offspring designs. Psychoneuroendocrinology 2006;31:1131–7.
[46] Bartels M, de Geus EJC, Kirschbaum C, Sluyter F, Boomsma DI. Heritability of daytime cortisol levels in children. Behav Genet 2003;33:421–33.
[47] Bartels M, Van den Berg M, Sluyter F, Boomsma DI, de Geus EJC. Heritability of cortisol levels: review and simultaneous analysis of twin studies. Psychoneuroendocrinology 2003;28: 121–37.
[48] Wüst S, Federenko I, Hellhammer DH, Kirschbaum C. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. Psychoneuroendocrinology 2000;25:707–20.
[49] Kirschbaum C, Pirke KM, Hellhammer DH. The Trier Social Stress Test—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993; 28:76–81.
[50] Larzul C, Foury A, Terenina E, Billon Y, Mormede P. Genetic parameters for ACTH response in pig. In: *German Society for Animal Science*. Geissen, Germany: 9th ed World Congress on Genetics Applied to Livestock Production; 2010: paper 0169.
[51] Levine S, Treiman DM. Differential plasma corticosterone response to stress in four inbred strains of mice. Endocrinology 1964;75:142–4.
[52] Shanks N, Griffiths J, Zalcman S, Zacharko RM, Anisman H. Mouse strain differences in plasma corticosterone following uncontrollable footshock. Pharmacol Biochem Behav 1990;36: 515–9.
[53] Jones BC, Sarrieau A, Reed CL, Azar MR, Mormède P. Contribution of sex and genetics to neuroendocrine adaptation to stress in mice. Psychoneuroendocrinology 1998;23:505–17.
[54] Castanon N, Hendley ED, Fan XM, Mormède P. Psychoneuroendocrine profile associated with hypertension or hyperactivity in spontaneously hypertensive rats. Am J Physiol 1993; 265:R1304–10.
[55] Castanon N, Mormede P. Psychobiogenetics: adapted tools for the study of the coupling between behavioral and neuroendocrine traits of emotional reactivity. Psychoneuroendocrinology 1994;19:257–82.
[56] Armario A, Gavaldà A, Martí J. Comparison of the behavioural and endocrine response to forced swimming stress in five inbred strains of rats. Psychoneuroendocrinology 1995;20: 879–90.
[57] Gómez F, de Kloet ER, Armario A. Glucocorticoid negative feedback on the HPA axis in five inbred rat strains. Am J Physiol 1998;274:R420–7.
[58] Gómez F, Lahmame A, De Kloet ER, Armario A. Hypothalamic-pituitary-adrenal response to chronic stress in five inbred rat strains: differential responses are mainly located at the adrenocortical level. Neuroendocrinology 1996;63:327–37.
[59] Marti J, Armario A. Forced swimming behavior is not related to the corticosterone levels achieved in the test: a study with four inbred rat strains. Physiol Behav 1996;59:369–73.
[60] Sarrieau A, Mormède P. Hypothalamic-pituitary-adrenal axis activity in the inbred brown Norway and Fischer 344 rat strains. Life Sci 1998;62:1417–25.
[61] Sarrieau A, Chaouloff F, Lemaire V, Mormède P. Comparison of the neuroendocrine responses to stress in outbred, inbred and F1 hybrid rats. Life Sci 1998;63:87–96.
[62] Huff G, Huff W, Rath N, Donoghue A, Anthony N, Nestor K. Differential effects of sex and genetics on behavior and stress response of turkeys. Poult Sci 2007;86:1294–303.
[63] Kowalski A, Mormède P, Jakubowski K, Jedlińska-Krakowska M. Comparison of susceptibility to stress in two genetic lines of turkey broilers, but-9 and big-6. Pol J Vet Sci 2002;5:145–50.
[64] Mormede P, Dantzer R, Bluthe RM, Caritez JC. Differences in adaptive abilities of 3 breeds of Chinese pigs—behavioral and neuroendocrine studies. Genet Sel Evol 1984;16:85–101.
[65] García-Belenguer S, Palacio J, Gascón M, Aceña C, Revilla R, Mormède P. Differences in the biological stress responses of two cattle breeds to walking up to mountain pastures in the Pyrenees. Vet Res 1996;27:515–26.
[66] Bergeron R, Gonyou HW, Eurell TE. Behavioral and physiological responses of Meishan, yorshire and crossbred gilts to conventional and turn-around gestation stalls. Can J Anim Sci 1996;76:289–97.
[67] Désautés C, Bidanel JP, Mormède P. Genetic study of behavioral and pituitary-adrenocortical reactivity in response to an environmental challenge in pigs. Physiol Behav 1997;62:337–45.

[68] Hay M, Mormède P. Urinary excretion of catecholamines, cortisol and their metabolites in Meishan and Large White sows: validation as a non-invasive and integrative assessment of adrenocortical and sympathoadrenal axis activity. Vet Res 1998;29:119–28.
[69] Engelbrecht Y, Herselman T, Louw A, Swart P. Investigation of the primary cause of hypoadrenocorticism in South African angora goats (Capra aegagrus): a comparison with Boer goats (Capra hircus) and merino sheep (Ovis aries). J Anim Sci 2000;78:371–9.
[70] Engelbrecht Y, Swart P. Adrenal function in angora goats: a comparative study of adrenal steroidogenesis in angora goats, Boer goats, and merino sheep. J Anim Sci 2000;78:1036–46.
[71] Fevolden S, Refstie T, Gjerde B. Genetic and phenotypic parameters for cortisol and glucose stress response in Atlantic salmon and rainbow trout. Aquaculture 1993;118:205–16.
[72] Fevolden S, Roed K, Fjalestad K, Stien J. Poststress levels of lysozyme and cortisol in adult rainbow trout: heritabilities and genetic correlations. J Fish Biol 1999;54:900–10.
[73] Redei EE. Molecular genetics of the stress-responsive adrenocortical axis. Ann Med 2008;40:139–48.
[74] Marissal-Arvy N, Lombès M, Petterson J, Moisan MP, Mormède P. Gain of function mutation in the mineralocorticoid receptor of the brown Norway rat. J Biol Chem 2004; 279:39232–9.
[75] Marissal-Arvy N, Mormède P. Effects of adrenalectomy and of mineralocorticoid receptor/glucocorticoid receptor ligands in female Brown Norway and Fischer 344 rats and F1 hybrids. J Neuroendocrinol 2002;14:574–9.
[76] Marissal-Arvy N, Mormède P. Excretion of electrolytes in Brown Norway and Fischer 344 rats: effects of adrenalectomy and of mineralocorticoid and glucocorticoid receptor ligands. Exp Physiol 2004;89:753–65.
[77] Marissal-Arvy N, Mormède P, Sarrieau A. Strain differences in corticosteroid receptor efficiencies and regulation in Brown Norway and Fischer 344 rats. J Neuroendocrinol 1999;11:267–73.
[78] Marissal-Arvy N, Ribot E, Sarrieau A, Mormède P. Is the mineralocorticoid receptor in Brown Norway rats constitutively active? J Neuroendocrinol 2000;12:576–88.
[79] Kosten TA, Ambrosio E. HPA axis function and drug addictive behaviors: insights from studies with Lewis and Fischer 344 inbred rats. Psychoneuroendocrinology 2002;27:35–69.
[80] Harizi H, Homo-Delarche F, Amrani A, Coulaud J, Mormède P. Marked genetic differences in the regulation of blood glucose under immune and restraint stress in mice reveals a wide range of corticosensitivity. J Neuroimmunol 2007;189:59–68.
[81] Harizi H, Mormède P, Corcuff JB. Inter-strain differences in glucocorticoid and mineralocorticoid effects on macrophage and lymphocyte functions in mice. J Neuroimmunol 2008;204: 38–42.
[82] Garlow SJ, Boone E, Li W, Owens MJ, Nemeroff CB. Genetic analysis of the hypothalamic corticotropin-releasing factor system. Endocrinology 2005;146:2362–8.
[83] Canario L, Billon Y, Caritez JC, Bidanel JP, Laloe D. Comparison of sow farrowing characteristics between a Chinese breed and three French breeds. Livest Sci 2009;125:132–40.
[84] Canario L, Cantoni E, Le Bihan E, et al. Between-breed variability of stillbirth and its relationship with sow and piglet characteristics. J Anim Sci 2006;84:3185–96.
[85] Bidanel JP. Estimation of crossbreeding parameters between Large White and Meishan porcine breeds. 3. Dominance and epistatic components of heterosis on reproductive traits. Genet Sel Evol 1993;25:263–81.
[86] Bidanel JP, Caritez JC, Legault C. Estimation of crossbreeding parameters between Large White and Meishan porcine breeds. 1. Reproductive performance. Genet Sel Evol 1989;21:507–26.
[87] Bidanel JP, Caritez JC, Gruand J, Legault C. Growth, carcass and meat quality performance of crossbred pigs with graded proportions of Meishan genes. Genet Sel Evol 1993;25:83–99.
[88] Bidanel JP, Caritez JC, Legault C. Estimation of crossbreeding parameters between Large White and Meishan porcine breeds. 2. Growth before weaning and growth of females during the growing and reproductive periods. Genet Sel Evol 1990;22: 431–45.
[89] Désautés C, Sarrieau A, Caritez JC, Mormède P. Behavior and pituitary-adrenal function in Large White and Meishan pigs. Domest Anim Endocrinol 1999;16:193–205.
[90] Weiler U, Claus R, Schnoebelen-Combes S, Louveau I. Influence of age and genotype on endocrine parameters and growth performance: a comparative study in wild boars, Meishan and Large White boars. Livest Prod Sci 1998;54:21–31.
[91] Wise T, Klindt J, Howard HJ, Conley AJ, Ford JJ. Endocrine relationships of Meishan and White composite females after weaning and during the luteal phase of the estrous cycle. J Anim Sci 2001;79:176–87.
[92] Foury A, Geverink NA, Gil M, et al. Stress neuroendocrine profiles in five pig breeding lines and the relationship with carcass composition. Animal 2007;1:973–82.
[93] Geverink NA, Foury A, Plastow GS, et al. Cortisol-binding globulin and meat quality in five European lines of pigs. J Anim Sci 2006;84:204–11.
[94] Guyonnet-Dupérat V, Geverink N, Plastow GS, et al. Functional implication of an arg307gly substitution in corticosteroid-binding globulin, a candidate gene for a quantitative trait locus associated with cortisol variability and obesity in pig. Genetics 2006;173:2143–9.
[95] Ousova O, Guyonnet-Duperat V, Iannuccelli N, et al. Corticosteroid binding globulin: a new target for cortisol-driven obesity. Mol Endocrinol 2004;18:1687–96.
[96] Hazard D, Liaubet L, Sancristobal M, Mormède P. Gene array and real time PCR analysis of the adrenal sensitivity to adrenocorticotropic hormone in pig. BMC Genomics 2008;9:101.
[97] Perreau V, Sarrieau A, Mormède P. Characterization of mineralocorticoid and glucocorticoid receptors in pigs: comparison of Meishan and Large White breeds. Life Sci 1999;64: 1501–15.
[98] Bradbury MJ, Akana SF, Dallman MF. Roles of type I and II corticosteroid receptors in regulation of basal activity in the hypothalamo-pituitary-adrenal axis during the diurnal trough and the peak: evidence for a nonadditive effect of combined receptor occupation. Endocrinology 1994;134:1286–96.
[99] de Kloet ER, Vreugdenhil E, Oitzl MS, Joëls M. Brain corticosteroid receptor balance in health and disease. Endocr Rev 1998;19:269–301.
[100] Ratka A, Sutanto W, Bloemers M, de Kloet ER. On the role of brain mineralocorticoid (type I) and glucocorticoid (type II) receptors in neuroendocrine regulation. Neuroendocrinology 1989;50:117–23.
[101] Désautés C, Bidanelt JP, Milant D, et al. Genetic linkage mapping of quantitative trait loci for behavioral and neuroendocrine stress response traits in pigs. J Anim Sci 2002;80: 2276–85.

[102] Fevolden S, Roed KH, Fjalestad KT. Selection response of cortisol and lysozyme in rainbow trout and correlation to growth. Aquaculture 2002;205:61–75.
[103] Pottinger TG, Carrick TR. Modification of the plasma cortisol response to stress in rainbow trout by selective breeding. Gen Comp Endocrinol 1999;116:122–32.
[104] Edens FW, Siegel HS. Adrenal responses in high and low ACTH response lines of chickens during acute heat stress. Gen Comp Endocrinol 1975;25:64–73.
[105] Gross WB, Siegel PB. Selective breeding of chickens for corticosterone response to social stress. Poult Sci 1985;64: 2230–3.
[106] Brown KI, Nestor KE. Some physiological responses of turkeys selected for high and low adrenal response to cold stress. Poult Sci 1973;52:1948–54.
[107] Satterlee DG, Johnson WA. Selection of Japanese quail for contrasting blood corticosterone response to immobilization. Poult Sci 1988;67:25–32.
[108] Touma C, Bunck M, Glasl L, et al. Mice selected for high versus low stress reactivity: a new animal model for affective disorders. Psychoneuroendocrinology 2008;33:839–62.
[109] Arnaud I. Thesis, *Variabilité Génétique des Réponses de Peur Chez le Canard*. Tours, France: INRA, Station de Recherches Avicole, Université François Rabelais; 2010.
[110] Pottinger TG, Carrick TR. ACTH does not mediate divergent stress responsiveness in rainbow trout. Comp Biochem Physiol A 2001;129:399–404.
[111] Li LA, Xia D, Wei S, Hartung J, Zhao RQ. Characterization of adrenal ACTH signaling pathway and steroidogenic enzymes in Erhualian and Pietrain pigs with different plasma cortisol levels. Steroids 2008;73:806–14.
[112] Li LA, Xia D, Wei S, Li X, Parvizi N, Zhao RQ. Diminished expression of ACTH signaling proteins and steroidogenic limiting factors in adrenocortical cells isolated from halothane nn pigs. Domest Anim Endocrinol 2008;35:1–7.
[113] Jouffe V, Rowe SJ, Liaubet L, et al. Using microarrays to identify positional candidate genes for QTL: the case study of ACTH response in pigs. BMC Proc 2009;3(S4):S14.
[114] Bureau C, Hennequet-Antier C, Couty M, Guémené D. Gene array analysis of adrenal glands in broiler chickens following ACTH treatment. BMC Genomics 2009;10:430.
[115] Hennessy DP, Jackson PN. Relationship between adrenal responsiveness and growth rate, In: Committee APSA, ed. *Manipulating Pig Production*. Perth, Australia: South; 1987:23.
[116] Knott SA, Cummins LJ, Dunshea FR, Leury BJ. Rams with poor feed efficiency are highly responsive to an exogenous adrenocorticotropin hormone (ACTH) challenge. Domest Anim Endocrinol 2008;34:261–8.
[117] Cafe LM, Robinson DL, Ferguson DM, McIntyre BL, Geesink GH, Greenwood PL. Cattle temperament: persistence of assessments and associations with productivity, efficiency, carcass and meat quality traits. J Anim Sci 2011;89:1452–65.
[118] Gilbert H, Bidanel JP, Gruand J, et al. Genetic parameters for residual feed intake in growing pigs, with emphasis on genetic relationships with carcass and meat quality traits. J Anim Sci 2007;85:3182–8.
[119] Remer T, Maser-Gluth C, Wudy SA. Glucocorticoid measurements in health and disease—metabolic implications and the potential of 24-h urine analyses. Mini Rev Med Chem 2008; 8:153–70.
[120] Geverink NA, Schouten WGP, Wiegant VM. Individual differences in behaviour, physiology and pathology in breeding gilts housed in groups or stalls. Appl Anim Behav Sci 2003;81:29–41.
[121] Richard E, Fernandez-Real J, Lopez-Bermejo A, et al. Corticosteroid binding globulin and glucocorticoid receptor genotypes influence body composition in a male population. Int J Genet Mol Biol 2009;1:59–63.
[122] Barat P, Duclos M, Gatta B, Roger P, Mormede P, Moisan MP. Corticosteroid binding globulin gene polymorphism influences cortisol driven fat distribution in obese women. Obes Res 2005;13:1485–90.
[123] Bright GM, Darmaun D. Corticosteroid-binding globulin modulates cortisol concentration responses to a given production rate. J Clin Endocrinol Metab 1995;80:764–9.
[124] Dhillo WS, Kong WM, Le Roux CW, et al. Cortisol-binding globulin is important in the interpretation of dynamic tests of the hypothalamic-pituitary-adrenal axis. Eur J Endocrinol 2002;146:231–5.
[125] Solberg LC, Baum AE, Ahmadiyeh N, et al. Genetic analysis of the stress-responsive adrenocortical axis. Physiol Genomics 2006;27:362–9.
[126] Moisan M-P. Genotype-phenotype associations in understanding the role of corticosteroid-binding globulin in health and disease animal models. Mol Cell Endocrinol 2010;316:35–41.
[127] Petersen HH, Andreassen TK, Breiderhoff T, et al. Hyporesponsiveness to glucocorticoids in mice genetically deficient for the corticosteroid binding globulin. Mol Cell Biol 2006; 26:7236–45.
[128] Richard EM, Helbling JC, Tridon C, et al. Plasma transcortin influences endocrine and behavioral stress responses in mice. Endocrinology 2010;151:649–59.
[129] Breuner CW, Orchinik M. Plasma binding proteins as mediators of corticosteroid action in vertebrates. J Endocrinol 2002; 175:99–112.
[130] Perogamvros I, Aarons L, Miller AG, Trainer PJ, Ray DW. Corticosteroid-binding globulin regulates cortisol pharmacokinetics. Clin Endocrinol (Oxf) 2011;74:30–6.
[131] DeRijk RH. Single nucleotide polymorphisms related to HPA axis reactivity. Neuroimmunomodulation 2009;16:340–52.
[132] Niu NF, Manickam V, Kalari KR, et al. Human glucocorticoid receptor alpha gene (nr3c1) pharmacogenomics: gene resequencing and functional genomics. J Clin Endocrinol Metab 2009;94:3072–84.
[133] Mormede P, Foury A, Barat P, et al. Molecular genetics of hypothalamic-pituitary-adrenal axis activity and function. Ann N Y Acad Sci 2011;1220:127–36.
[134] Marissal-Arvy N, Gaumont A, Langlois A, et al. Strain differences in hypothalamic pituitary adrenocortical axis function and adipogenic effects of corticosterone in rats. J Endocrinol 2007;195:473–84.
[135] Marissal-Arvy N, Langlois A, Tridon C, Mormede P. Functional variability in corticosteroid receptors is a major component of strain differences in fat deposition and metabolic consequences of enriched diets in rat. Metab Clin Exp 2011;60: 706–19.
[136] Muráni E, Ponsuksili S, D'Eath RB, et al. Association of HPA axis-related genetic variation with stress reactivity and aggressive behaviour in pigs. BMC Genet 2010;11:74.
[137] Tasker JG, Herman JP. Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic-pituitary-adrenal axis. Stress 2011;14:398–406.
[138] Walker JJ, Terry JR, Tsaneva-Atanasova K, Armstrong SP, McArdle CA, Lightman SL. Encoding and decoding mecha-

nisms of pulsatile hormone secretion. J Neuroendocrinol 2010;22:1226–38.
[139] Hay M, Meunier-Salaün MC, Brulaud F, Monnier M, Mormède P. Assessment of hypothalamic-pituitary-adrenal axis and sympathetic nervous system activity in pregnant sows through the measurement of glucocorticoids and catecholamines in urine. J Anim Sci 2000;78:420–8.
[140] Foury A, Devillers N, Sanchez MP, Griffon H, Le Roy P, Mormède P. Stress hormones, carcass composition and meat quality in large White × Duroc pigs. Meat Sci 2005;69:703–7.
[141] Lebret B, Meunier-Salaün MC, Foury A, Mormède P, Dransfield E, Dourmad JY. Influence of rearing conditions on performance, behavioral, and physiological responses of pigs to preslaughter handling, carcass traits, and meat quality. J Anim Sci 2006;84:2436–47.
[142] Lebret B, Prunier A, Bonhomme N, Foury A, Mormède P, Dourmad JY. Physiological traits and meat quality of pigs as affected by genotype and housing system. Meat Sci 2011;88: 14–22.
[143] Foury A, Lebret B, Chevillon P, Vautier A, Terlouw C, Mormède P. Alternative rearing systems in pigs: consequences on stress indicators at slaughter and meat quality. Animal 2011;5:1620–5.
[144] Cole SW. Elevating the perspective on human stress genomics. Psychoneuroendocrinology 2010;35:955–62.
[145] O'Donovan A, Sun B, Cole S, et al. Transcriptional control of monocyte gene expression in post-traumatic stress disorder. Dis Markers 2011;30:123–32.
[146] Mormède P, Courvoisier H, Ramos A, et al. Molecular genetic approaches to investigate individual variations in behavioral and neuroendocrine stress responses. Psychoneuroendocrinology 2002;27:563–83.
[147] Ciaranello RD. Regulation of phenylethanolamine n-methyltransferase. Biochem Pharmacol 1978;27:1895–7.
[148] Heo J, Kattesh HG, Roberts MP, Schneider JF. Plasma levels of cortisol and corticosteroid-binding globulin (CBG) and hepatic CBG mRNA expression in pre- and postnatal pigs. Domest Anim Endocrinol 2003;25:263–73.
[149] First NL, Bosc MJ. Proposed mechanisms controlling parturition and the induction of parturition in swine. J Anim Sci 1979;48:1407–21.
[150] Liggins GC. The role of cortisol in preparing the fetus for birth. Reprod Fertil Dev 1994;6:141–50.
[151] Kattesh HG, Baumbach GA, Gillespie BB, Schneider JF, Murai JT. Distribution between protein-bound and free forms of plasma cortisol in the gilt and fetal pig near term. Biol Neonate 1997;72:192–200.
[152] Randall GCB. Changes in the concentrations of corticosteroids in the blood of fetal pigs and their dams during late gestation and labor. Biol Reprod 1983;29:1077–84.
[153] Klemcke HG. Ontogenetic changes in porcine adrenocortical adrenocorticotropic hormone receptors. Int J Biochem 1992; 24:79–84.
[154] Silver M, Fowden AL. Pituitary adrenocortical activity in the fetal pig in the last 3rd of gestation. Q Jour Exp Physiol Cogn Med Sci 1989;74:197–206.
[155] Mayor F, Cuezva JM. Hormonal and metabolic changes in the perinatal period. Biol Neonate 1985;48:185–96.
[156] van der Lende T, Knol EF, Leenhouwers JI. Prenatal development as a predisposing factor for perinatal losses in pigs. Reprod Suppl 2001;58:247–61.
[157] Fowden AL, Apatu RSK, Silver M. The glucogenic capacity of the fetal pig: developmental regulation by cortisol. Exp Physiol 1995;80:457–67.
[158] Steinhoff-Wagner J, Görs S, Junghans P, et al. Maturation of endogenous glucose production in preterm and term calves. J Dairy Sci 2011;94:5111–23.
[159] Herpin P, Damon M, Le Dividich J. Development of thermoregulation and neonatal survival in pigs. Livest Prod Sci 2002; 78:25–45.
[160] Herpin P, Lossec G, Schmidt I, et al. Effect of age and cold exposure on morphofunctional characteristics of skeletal muscle in neonatal pigs. Pflugers Arch 2002;444:610–8.
[161] Leenhouwers JI, Knol EF, van der Lende T. Differences in late prenatal development as an explanation for genetic differences in piglet survival. Livest Prod Sci 2002;78:57–62.
[162] Leenhouwers JI, Knol EF, de Groot PN, Vos H, van der Lende T. Fetal development in the pig in relation to genetic merit for piglet survival. J Anim Sci 2002;80:1759–70.
[163] Bollen M, Keppens S, Stalmans W. Specific features of glycogen metabolism in the liver. Biochem J 1998;336 (Pt 1):19–31.
[164] Sangild PT, Sjöström H, Norén O, Fowden AL, Silver M. The prenatal development and glucocorticoid control of brush-border hydrolases in the pig small intestine. Pediatr Res 1995; 37:207–12.
[165] Sangild PT, Fowden AL, Trahair JF. How does the foetal gastrointestinal tract develop in preparation for enteral nutrition after birth? Livest Prod Sci 2000;66:141–50.
[166] Klemcke HG, Christenson RK. Porcine fetal and maternal adrenocorticotropic hormone and corticosteroid concentrations during gestation and their relation to fetal size. Biol Reprod 1997;57:99–106.
[167] Michel V, Peinnequin A, Alonso A, Buguet A, Cespuglio R, Canini F. Decreased heat tolerance is associated with hypothalamo-pituitary-adrenocortical axis impairment. Neuroscience 2007;147:522–31.
[168] Michel V, Peinnequin A, Alonso A, Buguet A, Cespuglio R, Canini F. Effect of glucocorticoid depletion on heat-induced hsp70, IL-1beta and TNF-alpha gene expression. Brain Res 2007;1164:63–71.
[169] Soleimani AF, Zulkifli I, Omar AR, Raha AR. Physiological responses of 3 chicken breeds to acute heat stress. Poult Sci 2011;90:1435–40.
[170] Gross WB. Plasma steroid tendency, social environment and Eimeria necatrix infection. Poult Sci 1976;55:1508–12.
[171] Minozzi G, Parmentier HK, Mignon-Grasteau S, et al. Correlated effects of selection for immunity in white leghorn chicken lines on natural antibodies and specific antibody responses to KLH and m-butyricum. BMC Genet 2008;9.
[172] Rauw WM, Kanis E, Noordhuizen-Stassen EN, Grommers FJ. Undesirable side effects of selection for high production efficiency in farm animals: a review. Livest Prod Sci 1998;56:15–33.
[173] Star L, Ellen ED, Uitdehaag K, Brom FWA. A plea to implement robustness into a breeding goal: poultry as an example. J Agric Environ Ethics 2008;21:109–25.
[174] Siegel PB, Honaker CF, Rauw WM. Selection for high production in poultry, In: Rauw WM, ed. *Resource Allocation Theory Applied to Farm Animal Production*. Wallingford, UK: CABI; 2009: 230–42.
[175] Veerkamp RF, Windig JJ, Calus MPL, Ouweltjes W, de Haas Y, Beerda B. Selection for high production in dairy cattle, In:

Rauw WM, ed. *Resource Allocation Theory Applied to Farm Animal Production*. Wallingford, UK: CABI; 2009:243–60.

[176] Beilharz RG. Environmental limit to genetic change. An alternative theorem of natural selection. J Anim Breed Genetz Tierz Zungt Biol 1998;115:433–7.

[177] Trade-offs GDDRauw WM, ed. *Resource Allocation Theory Applied to Farm Animal Production*. Wallingford, UK: CABI; 2009: 44–60.

[178] Knap PW, Rauw WM. Selection for high production in pigs. In: Rauw WM, ed. *Resource Allocation Theory Applied to Farm Animal Production*. Wallingford, UK: CABI; 2009: 210–29.

[179] Knap PW, Su G. Genotype by environment interaction for litter size in pigs as quantified by reaction norms analysis. Animal 2008;2:1742–7.

[180] Bodin L, Bolet G, Garcia M, Garreau H, Larzul C, David I. Robustesse et canalisation: vision de geneticiens [Canalisation and robustness: the geneticist insight]. Inra Prod Anim 2010; 23:11–21.

[181] Lankin V. Factors of diversity of domestic behaviour in sheep. Genet Sel Evol 1997;29:73–92.

[182] Lankin VS. Domestic behavior in sheep: the role of behavioral polymorphism in the regulation of stress reactions. Rus J Genet 1999;35:952–9.

[183] Lankin VS, Stakan GA, Naumenko EV. Domestic behavior of sheep. 1. Relation of the functional-state of the hypothalamic-pituitary-adrenal system to behavior and age in thin-fleeced sheep. Genetika 1979;15:891–900.

[184] Lankin VS, Stakan GA, Naumenko EV. Domestic behavior of sheep. 3. Hereditary determination of the endocrine function of the pituitary-adrenal system in thin-fleeced sheep with different behavior type. Genetika 1980;16:1089–95.

[185] Künzl C, Kaiser S, Meier E, Sachser N. Is a wild mammal kept and reared in captivity still a wild animal? Horm Behav 2003; 43:187–96.

[186] Gulevich RG, Oskina IN, Shikhevich SG, Fedorova EV, Trut LN. Effect of selection for behavior on pituitary-adrenal axis and proopiomelanocortin gene expression in silver foxes (Vulpes vulpes). Physiol Behav 2004;82:513–8.

[187] Albert FW, Shchepina O, Winter C, et al. Phenotypic differences in behavior, physiology and neurochemistry between rats selected for tameness and for defensive aggression towards humans. Horm Behav 2008;53:413–21.

[188] Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev 2005;29:3–38.

[189] Foury A, Tribout T, Bazin C, et al. Estimation of genetic trends from 1977 to 2000 for stress-responsive systems in French Large White and landrace pig populations using frozen semen. Animal 2009;3:1681–7.