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Breeding for robustness: the role of cortisol*

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Robustness in farm animals was defined by Knap as 'the ability to combine a high production potential with resilience to stressors, allowing for unproblematic expression of a high production potential in a wide variety of environmental conditions'. The importance of robustness-related traits in breeding objectives is progressively increasing towards 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 in various stages. It is also possible to use global evaluation of sensitivity to the environment (e.g. reaction norm analysis or canalization), but these techniques are difficult to implement in practice. The hypothalamic–pituitary–adrenocortical (HPA) axis is the most important stress-responsive neuroendocrine system. Cortisol (or corticosterone) released by the adrenal cortices exerts a large range of effects on metabolism, the immune system, inflammatory processes and brain function, for example. Large individual variations have been described in the HPA 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 traits related to robustness and adaptation. For instance, newborn survival was shown to be directly related to plasma cortisol levels at birth, resistance to bacteria and parasites are increased in animals selected for a higher HPA axis response to stress, and tolerance to heat stress is better in those animals that are able to mount a strong stress response. Intense selection for lean tissue growth during the last decades has concomitantly reduced cortisol production, which may be responsible for the negative effects of selection on piglet survival. One strategy to improve robustness is to select animals with higher HPA axis activity. Several sources of genetic polymorphism have been described in the HPA axis. Hormone production by the adrenal cortices under stimulation by adrenocorticotropin hormone is a major source of individual differences. Several candidate genes have been identified by genomic studies and are currently under investigation. Bioavailability of hormones as well as receptor and post-receptor mechanisms are also subject to individual variation. Integration of these different sources of genetic variability will allow the development of a model for marker-assisted selection to improve animal robustness without negative side effects on production traits.

Keywords: stress, robustness, cortisol, genetics, marker-assisted selection

Implications

Genetic and genomic studies, combined with a systems genetic approach, will deliver a model of the genetic architecture of the stress-responsive neuroendocrine hypothalamic–pituitary–adrenocortical axis as related to production and robustness traits. This model will generate molecular markers to be used in the selection of more robust animals and improved welfare with limited consequences on production traits.

Introduction

Genetic selection in farm animals aims at optimizing the efficiency of production by increasing production level and product quality, and by reducing production costs (e.g. feed efficiency). However, the genetic potential of animals is usually not fully expressed in commercial conditions, due to the limiting influence of the environment. Robustness is the specific quality of an individual to express a high-production potential in a wide variety of environmental conditions and is now a specific breeding goal in the context of sustainable farm animal breeding. In this review paper, we explore the various strategies used to increase robustness, and more specifically the possible use of genetic variation in the

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hypothalamic–pituitary–adrenocortical axis, the main neuroendocrine system involved in adaptation to stress.

Robustness

The concept of robustness in farm animals was defined by Knap (2005) as 'the ability to combine a high production potential with resilience to stressors, allowing for unproblematic expression of a high production potential in a wide variety of environmental conditions'. Indeed, genetic progress in production traits realized at the nucleus level may become constrained in commercial practice if the resulting animals (end products of the breeding system) are raised in conditions that do not support full expression of their genetic potential. Robustness may then be seen as a global measure – as evaluated, for instance, by the realized level or functional longevity – of the sensitivity of the animal to the climatic, physical, nutritious, infectious and social environment, and to the metabolic load of its genetic potential for production traits. This concept also includes traits that are specifically sensitive to inadequate environmental conditions, such as skeletal and cardiovascular integrity, disease resistance and mortality in various stages, altogether known as 'functional traits'. Such traits are important not only in terms of performance levels but also for animal health and welfare (Knap, 2009).

Robustness as a breeding goal

In its 'Sustainable Farm Animal Breeding and Reproduction, a vision for 2025', the FABRE Technology Platform (2006; http://www.fabretp.org/images/vision.fabretp.def1.pdf) described the farm animal of the future as 'robust, adapted and healthy'. The importance of robustness-related traits in breeding objectives is progressively increasing towards 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. As stated by Knap (2009), 'Sustainable breeding goals combine robustness traits with production traits to such an extent that selection balances genetic change in production potential with genetic change in environmental sensitivity'. Indeed, when selection focuses on production traits only, the above-mentioned functional traits are likely to become compromised (Rauw *et al*., 1998; Star *et al*., 2008; Knap and Rauw, 2009; Siegel *et al*., 2009; Veerkamp *et al*., 2009). The current evolution of animal production systems (increase of economic pressure, diversification of production environments, reduction of individual animal management, increase of parasitic load with outdoor production) combined with global warming, increases the importance of adaptation and robustness traits in sustainable breeding goals.

Genetic strategies towards robust animals

Several breeding strategies can be implemented to increase robustness: Global sensitivity to the environment is measured by techniques such as the reaction norm analysis by comparing animals with identical genotypes in different environments (Knap and Su, 2008). This is a difficult endeavour and heritability of the character is low. Sensitivity to the environment may also contribute to the environmental variance of a trait, which has been shown to be under genetic control (SanCristobal-Gaudy *et al*., 2001; Sorensen and Waagepetersen, 2003; Ros *et al*., 2004; Mulder *et al*., 2007 and 2008; Mulder *et al*., 2009). The reduction of trait variance by genetic selection is also known as canalizing selection or canalization (SanCristobal-Gaudy *et al*., 1998; Bolet *et al*., 2007; Garreau *et al*., 2008; Bodin *et al*., 2010).

Another strategy is direct selection for robustness-related traits. Genetic improvement in functional traits, such as leg soundness, mortality rates in various stages of the animal's life and functional longevity is possible when these traits are properly included into breeding goals and selection criteria, and is being realized in existing breeding programmes (Knap, 2009). Disease resistance traits are more difficult to select for, except in specific cases such as the somatic cell count in milk that is a good indicator of sensitivity to mammary infections in dairy cattle (Colleau and Regaldo, 2001). Current efforts towards the discovery of molecular bases for genetic variation of these complex traits will possibly deliver DNA polymorphisms to be used for genomic selection.

The third strategy that will be developed in this paper focuses on the molecular genetics of neuroendocrine stress responses, more specifically the hypothalamic–pituitary–adrenocortical (HPA) axis.

The HPA axis

The HPA axis is the cornerstone of biological stress responses, together with the autonomic nervous system, in concert with behavioural adaptive processes. The main output elements of the axis are the glucocorticoid (GR) hormones, cortisol (mammals, fish) or corticosterone (birds) synthesized in and released by the adrenal cortex in response to the adrenocorticotropin hormone (ACTH) released by the anterior pituitary gland under the control of hypothalamic neurohormones corticotrophin-releasing hormone (CRH) and vasopressin. GR hormones act on a wide range of cells and tissues via the GR and mineralocorticoid nuclear receptors. They influence numerous metabolic pathways, the immune system, inflammatory processes and brain functions, to mention the most important. They also exert a strong feedback on the HPA axis (Chrousos, 1998).

Cortisol, production and robustness

Cortisol and production traits

Cortisol has complex, and mostly negative, effects on production traits. Hennessy *et al*. (1988) showed that the adrenal response to ACTH in pigs is an individual trait and that growth rate and feed efficiency are negatively related to the intensity of this response (Hennessy and Jackson, 1987). Similar results have been obtained in sheep, with residual

feed intake being directly proportional to the release of cortisol after injection of ACTH (Knott *et al*., 2008). An extensive study of the effects of corticosterone in chickens chronically infused with ACTH describes the effects of adrenal stimulation on production (e.g. reduced feed intake, body and carcass weight) and physiological (e.g. increased liver weight and lipid content, increased adrenal glands weight and plasma concentrations of glucose and lipids) traits (Puvadolpirod and Thaxton, 2000a, 2000b, 2000c and 2000d; Thaxton and Puvadolpirod, 2000). In pigs, several examples show that leanness is influenced by the cortisol production rate as measured, for instance, by the excretion level in urine (Foury *et al*., 2005 and 2007). All these changes result mainly from the physiological effects of GR hormones on metabolism, with an increase of energy storage (fat and glycogen) at the expense of tissue proteins (Devenport *et al*., 1989).

Cortisol and robustness

By contrast, several lines of evidence show that cortisol has positive effects on robustness traits, although experimental data are still fragmentary, especially in farm animal species. GR hormones strengthen adaptation processes. Michel *et al*. (2007b) studied individual variations in responses to heat stress in rats. The animals with the strongest HPA 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 haemoconcentration, and a reduced inflammatory response in the brain. These differences reflect the physiological effects of GR hormones (Michel *et al*., 2007a) and show that the animals that mount a strong stress response adapt better to the stressor. The generalization of these results to other stress stimuli is still to be demonstrated.

Another example of the positive influence of stress hormones on robustness traits can be found in the work on newborn piglet survival by Leenhouwers *et al*. (2002), who showed that piglet viability is a heritable and piglet-intrinsic trait. 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 liver and muscle that reflects the gluconeogenetic properties of cortisol (Mayor and Cuezva, 1985). Indeed, during the final days of gestation, there is a surge of HPA axis activity in the foetus (Silver and Fowden, 1989; Kattesh *et al*., 1990; Heo *et al*., 2003) that mediates, together with insulin, liver glycogen accumulation during the late foetal stage (Bollen *et al*., 1998). Large differences in metabolic traits have been described among pig breeds (Hoffman *et al*., 1983), suggesting a role of genetic factors. This mechanism may at least partly explain the exceptional viability of Meishan piglets (Canario *et al*., 2009), as this breed displays a high activity of the HPA axis (Klemcke and Christenson, 1997; Désautés *et al*., 1999).

Finally, experimental evidence in poultry shows that genetic selection for the intensity of the HPA 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 (Gross, 1976). Recently, Minozzi *et al*. (2008) 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 immune traits were correlated with the level of several 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 (Minozzi *et al*., 2008). These differences reflect the complex effects of corticosteroid hormones on the immune system and inflammatory processes (Salak-Johnson and McGlone, 2007; Marketon and Glaser, 2008).

Altogether, these data suggest that GRs have a positive influence on several robustness-related traits. Considering the above-mentioned general development towards less supportive production conditions, this positive influence is worth being explored in more detail.

Cortisol: trade-off factor between production and robustness

It is common sense that robustness and production levels do not go along together very well. Local breeds, well adapted to their (eventually harsh) environment have usually low absolute levels of production, although it may be high considering the environmental constraints. By contrast, genetically selected, highly productive stocks frequently show signs of reduced robustness (Rauw *et al*., 1998; Star *et al*., 2008; Knap and Rauw, 2009; Siegel *et al*., 2009; Veerkamp *et al*., 2009). This trade-off between productivity and robustness is predicted by the resource allocation theory (Beilharz, 1998; Glazier, 2009) – the energetic resources of an individual are limited and their allocation across metabolic functions is optimized towards the best adaptation of the individual to its environment (= fitness). Genetic selection for production traits logically redirects resources towards those production traits, at the expense of other traits (such as robustness traits). When resources are not sufficient to support full expression of the production potential, this becomes problematic, and leads to genotype × environment interaction.

The HPA axis is primarily a neuroendocrine system involved in numerous physiological regulations. Its implication in stress responses results from its ability to mobilize energy to support adaptation, but this catabolic activity is

exerted at the expense of anabolism-based production potential. Therefore, the effects of cortisol on production and robustness traits as described in the previous paragraphs are two facets of the role of the HPA axis in homeostasis and adaptation, but it appears that these effects of cortisol may be antagonistic. Recently, in the French Large White pig breed, a comparison of progeny from sires born in 1977 (frozen semen) *v.* 1998 to 2000 (Foury *et al*., 2009) showed a decrease of the production of cortisol (urinary cortisol at slaughter), together with an improvement of production traits (growth rate, feed efficiency, leanness). This trend illustrates the above-mentioned negative effect of cortisol on production traits, so that HPA axis activity was counter selected in the selection process for production traits. As a consequence, this decrease in HPA axis activity may explain part of the compromised robustness that coincides with over-focused genetic improvement of production traits in farm animals.

Therefore, the HPA axis appears as a putative physiological element of the trade-off between production and robustness traits, which cortisol influences negatively and positively, respectively. Hence, an additional strategy to those listed above to increase farm animal robustness would be to strengthen the HPA axis activity, but without the possible side effect of increased cortisol production to compromise productivity. This objective does not appear to be out of reach. Indeed, the functional variability of the HPA axis is usually very large, even in genetically homogeneous populations. Foury *et al*. (2007) found a 30-fold range of urine cortisol concentrations in each of five pure pig lines, much more than the variation of production traits. In the above-mentioned study of genetic trends of stress-responsive systems in the French Large White, (Foury *et al*., 2009) found a -0.27 correlation between cortisol levels (in urine collected from the bladder after slaughter) and carcass lean content, so that only $0.27 \times 0.27 = 7.3\%$ of the variance of leanness is related to differences in cortisol production. It is therefore possible to envisage the selection for a stronger HPA axis to improve robustness without compromising production traits. Indeed, it was previously shown that the introduction of 'functional traits' in selection programmes could efficiently improve robustness without compromising the genetic gain on production traits (Knap, 2009).

Genetics and the HPA axis

Genetics of stress responses

Basal activity of the HPA axis and the response to stress are strongly influenced by genetic factors (Mormede *et al*., 2002; Redei, 2008; DeRijk, 2009). Pig populations show much functional variation (e.g. (Geverink *et al*., 2006; Foury *et al*., 2007)) and divergent genetic selection for the HPA axis response to various stimuli has been successful in a wide range of species: trout (confinement stress: (Fevolden *et al*., 1999; Pottinger and Carrick, 1999), chickens (adrenal response to ACTH: (Edens and Siegel, 1975); social stress: (Gross and Siegel, 1985), turkeys (cold stress: (Brown and Nestor, 1973), Japanese quail (immobilization stress: (Satterlee and Johnson, 1988) and mice (restraint stress: (Touma *et al*., 2008). The response to selection is usually very strong, with realized heritability between 0.4 and 0.5.

Adrenal cortex sensitivity to ACTH

Genetic variation is present in every component of the system, at the level of hormone production, bioavailability and action. The production rate of cortisol is primarily regulated by the sensitivity of the adrenal cortex to ACTH. Hennessy *et al*. (1988) demonstrated in pigs that the adrenal response to ACTH is variable among individuals but stable across time for a given animal. Similar differences in cortisol secretion were shown in response to CRH (Zhang *et al*., 1990), physical exercise or insulin-induced hypoglycaemia (Zhang *et al*., 1992), although the ACTH response was not different among individuals, so that the effect must have been due to adrenal sensitivity to ACTH. Metabolic clearance of cortisol bears no relationship with the response to ACTH (Zhang *et al*., 1993). Altogether, these data show that adrenal sensitivity to ACTH is a key index of individual differences in HPA function. As noted previously, the magnitude of the adrenal response to ACTH is negatively correlated with body weight and growth rate (Hennessy and Jackson, 1987), but did not show, in this paper, any relationship to body fat content or muscle pH. The adrenal response to ACTH is highly heritable ($h^2 = 0.51$; (Larzul *et al.,* 2010), data obtained in a Large White pig population). Indeed, as mentioned in the previous paragraph, Brown and Nestor (1973) could select divergent lines of turkey based on their response to ACTH injection, with a realized heritability of 0.28. The same kind of variability in adrenal response to ACTH has been shown in humans (Bertagna *et al*., 1994; Coste *et al*., 1994).

Differential gene expression studies in pigs (Hazard *et al*., 2008; Li *et al*., 2008a and 2008b; Jouffe *et al*., 2009) and chickens (Bureau *et al*., 2009) have produced candidate genes for differences in sensitivity to ACTH.

Bioavailability of GR hormones

Bioavailability of GR hormones is regulated by metabolic enzymes and carrier proteins. The enzymes 11β-hydroxysteroid dehydrogenase 1 and 2 convert cortisol and corticosterone into their inactive 11-oxo derivatives (type 2) and back (type 1). This mechanism is an important regulator of GR hormone activity (Remer *et al*., 2008). Although research in this field is very active towards the development of drugs for the control of obesity and metabolic diseases in humans (Hale and Wang, 2008), very little information is available in farm animals. An association between a single nucleotide polymorphism (SNP) in the *HSD11B1* gene and production traits has been described in two pig populations, although these effects may be not be due to the causative mutation (Otieno *et al*., 2005).

In plasma, GR hormones bind with high affinity to a specific glycoprotein, corticosteroid-binding globulin (CBG) and with a lower affinity to albumin, so that the free, active fraction of the hormones is small and highly regulated by CBG levels.

A genetic mapping experiment in an F2 intercross between Meishan and Large White pig breeds showed an association between a locus on pig chromosome 7q26 and cortisol levels, especially after the pigs were exposed to the stress of a novel environment (Desautes *et al.*, 2002). By comparative genomics, the gene encoding CBG (*SERPINA6*) appeared to be a good candidate, and further research strongly supported the implication of mutations in the *SERPINA6* gene in cortisolaemia, carcass composition and meat quality (Ousova *et al.*, 2004; Geverink *et al.*, 2006; Guyonnet-Duperat *et al.*, 2006). Several recent animal and human studies confirm the role of CBG or its genomic locus in traits related to neuropsychiatry, obesity and diabetes, immunity and inflammation, as well as growth (see Moisan, 2010, for a review).

Receptors and transduction mechanisms

Large genetic variations in the efficiency of corticosteroid hormones have been described (e.g. Harizi *et al.*, 2007, in mice). In humans and laboratory animals, numerous molecular variations have been described in the sequence of receptors, with functional consequences for health and disease (van Rossum and Lamberts, 2004; DeRijk, 2009), but very little information is available in farm animal species (Perreau *et al.*, 1999).

This review of the literature shows that GR secretion and function is highly variable due to numerous genetic differences in all the components of the HPA axis. Several molecular variations in gene structure have functional consequences on various traits related to stress responses, production and robustness. Data in farm animals are still incomplete, but research is active in this field. We also need more information about the systems genetics of the HPA axis for a more integrated understanding of its functioning and effects. Indeed, several sources of genetic variability are usually found in the same model (Marissal-Arvy *et al.*, 2004), but very little is known about the interactions among various sources of variability within the axis, and how they eventually compensate for or potentiate each other. Some data indicate that the effect of a single mutation (Carter *et al.*, 2009), or the consequence of GR hormone removal (de Jong *et al.*, 2007), is strongly dependent on genetic background. It is also necessary to explore the functional significance of various parameters classically used to evaluate HPA axis activity. For instance, when comparing the response of three 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 (Harizi *et al.*, 2007). At the present state of knowledge, selection should aim at an increase of cortisol production (sensitivity of the adrenal cortex to ACTH), of hormone bioavailability (via increased *SERPINA6* expression, for instance) and of transduction mechanisms efficiency. Modelling the various sources of genetic variability and their functional consequences should provide insight in the best use of DNA markers to influence the function of the HPA axis towards the breeding goals of improved robustness without negative effects on production traits.

It must be noticed here that cortisol concentrations does not generally equate to stress level: the relationship between the two is genotype-specific, depending on genetic influences on HPA axis function, not only in terms of cortisol production, as measured by hormone concentrations in plasma or other body fluids (saliva, urine, faeces), but also in the efficiency of cortisol effects on its targets, due to genetic influences on hormone bioavailability and receptor/post-receptor mechanisms. As a consequence, selection for higher HPA axis activity or functionality should not increase stress as measured by psycho-behavioural consequences of environmental stimuli (Dantzer and Mormede, 1983). Indeed, recent selection experiments in mice, based on their corticosterone response to restraint stress, showed that the low line (with lower corticosterone response to stress) displayed a 'depressed' behavioural phenotype and more aggressive tendencies (Touma *et al.*, 2008). It will be worth investigating in farm animals the changes in psycho-behavioural responses to stress as a result of the genetic selection towards a more active HPA axis.

Conclusions and perspectives

The HPA axis is a neuroendocrine system of critical importance in the regulation of energy metabolism and stress responses. Its level of activity influences production traits negatively and several robustness traits positively. The recent history of genetic selection for production traits such as growth rate, feed efficiency and leanness (all negatively influenced by GR hormones) has probably contributed to the reduction of HPA axis activity and consequently to a decrease of the robustness of modern, high-productivity animals. In the context of sustainable breeding, the genetic selection objective aims at a better balance between production and robustness traits. HPA axis activity should then be increased to improve robustness, but at the same time, the high production level of modern genotypes should not be compromised. It is very difficult to envisage phenotypic selection on HPA axis activity in farm animal populations, but marker-assisted selection may present a realistic alternative. A high genetic variability is present in the various components of the HPA axis. As with every other trait studied in livestock species, large numbers of genes are probably involved, and (particularly for these traits) they must be expected to interact intensively. Current developments in bioinformatics make it increasingly feasible to quantify the effects of very large numbers of polymorphisms (SNPs) on the phenotypes of interest (genomic prediction) and on their underlying mechanisms ('quantomics', www.quantomics.eu). The limiting factor in such approaches is an accurate estimation of the effect of each marker: this requires observations of the trait on large numbers of animals, updated regularly. But once this exercise is completed, the actual selection programme does not require phenotypic records anymore.

Such a selection strategy based on the genetic variation of neuroendocrine stress systems would be complementary to

quantitative approaches such as the integration of robustness phenotypes or environmental sensitivity in the selection programmes.

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