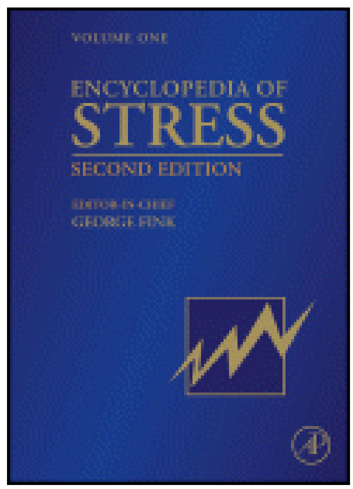

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highly aware populations studied so far. Based on the evidence to date, however, there is cause for cautious optimism that if attention is paid to providing high-quality information and support to at-risk families the potential medical benefits of genetic testing can be realized without causing emotional or behavioral harm.

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Genetic Variation of HPA Axis Activity and Function in Farm Animals

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Glossary

Corticosteroid-binding globulin (CBG)	A glycoprotein specifically carrying glucocorticoid hormone in blood plasma.
Genotype	The specific genetic makeup (the specific genome) of an individual. It codes for the phenotype of that individual.
Heritability	The proportion of the observed variation in a particular phenotype and, in a particular study, that can be attributed to the contribution of genotype (inheritance).
Hypothalamic-pituitary-adrenal (HPA) axis	The neuroendocrine system responsible for glucocorticoid hormone secretion.
Phenotype	A specific manifestation of a trait that varies between individuals. The phenotype is determined to some extent by genotype, or by the identity of the alleles that an individual carries at one or more positions on the chromosomes. Quantitative phenotypes are determined by multiple genes and are influenced by environmental factors.
Quantitative trait locus (QTL)	A polymorphic site on a chromosome containing alleles that differentially influence the expression of a quantitative trait.
Single nucleotide polymorphisms (SNPs)	Stable mutations consisting of a change at a single base in a DNA molecule. They are the most common type of genetic variation.

Evidence for Genetic Variability

A wide range of variability has been observed in hypothalamic-pituitary-adrenal (HPA) axis function, both basal and in response to stress. The contribution of genetic factors is shown by the differences among genetically defined stocks. Most available data have been obtained from pigs. Wild boars have the highest levels of cortisol, followed by Chinese breeds, including the most-studied Meishan. The highly selected lean breeds Large White and Landrace have the lowest levels, and Piétrain and Duroc pigs show intermediate levels. Few data are available in other species.

If a trait is influenced by genetic factors, it should be possible to increase or decrease the value of this trait by genetic selection. Indeed, divergent lines have been obtained by genetic selection in poultry (response to adrenocorticotropin [ACTH] or social stress), Japanese quail (response to immobilization), turkey (cold stress), and trout (confinement stress).

Sources of Genetic Variability

This article will not deal with major gene effects on HPA axis activity as seen in endocrine diseases induced by corticosteroid receptor or enzymatic defects. Traits such as circulating cortisol levels are normally distributed in genetically heterogeneous populations, suggesting that several genes may influence the phenotype, each gene with a small effect, and with complex gene × gene and gene × environment interactions. Several sources of genetic variability have been identified in farm animals.

Adrenal Sensitivity to ACTH

In the 1980s, D. P. Hennessy (Victoria, Australia) demonstrated in pigs that the increase of plasma cortisol after ACTH injection was variable among individuals but stable across time for a given animal. Similar differences in cortisol secretion were shown in response to corticotropin-releasing hormone (CRH), physical exercise, or insulin-induced hypoglycemia, although the release of ACTH was not different among individuals. Furthermore, the metabolic clearance of cortisol bears no relationship with the response to ACTH. Altogether, these data demonstrate that the key index of individual differences in HPA axis activity is the adrenal sensitivity to ACTH that was shown to be heritable in pigs. Several experimental results confirm genetic influences on the sensitivity of adrenal glands to ACTH. For instance, Meishan pigs (high cortisol levels) have a higher response to ACTH than Large Whites (low cortisol). In poultry, divergent lines could be selected on this trait. In quails, selection for high corticosterone to immobilization increased the steroidogenic response of adrenocortical cells to ACTH, and in turkeys, selection for a high corticosterone response to cold stress also increased the sensitivity of the adrenal gland to ACTH. In trout, the divergent cortisol response to confinement stress mostly results from the selection of animals with divergent interrenal gland response to ACTH, together with a large difference in the expression level of genes involved in corticosteroid hormone synthesis. Taken together, these data show that the adrenal sensitivity to ACTH is an important mechanism by which genetic factors influence HPA axis response to stress.

Hormone Bioavailability

Quantitative trait locus (QTL) analysis is a strategy to search for gene polymorphisms influencing a quantitative trait. It is based on the linkage between phenotypic value and genetic polymorphisms in a segregating population, usually an F2 intercross or a backcross. A QTL analysis run on an F2 intercross between the Large White and Meishan breeds revealed the large influence of a locus located at the end of the q arm of chromosome 7 on basal and post-stress (novel environment exposure) levels of cortisol, explaining, respectively, 7.7% and 20.7% of the phenotypic variance, with the Meishan alleles increasing cortisol levels. Other loci on chromosome 1 and 17 were shown to influence poststress ACTH levels. The comparison of genetic maps from different species shows that the end of the long arm of chromosome 7 is homologous to the telomeric end of the long arm of human chromosome 14. In this region corticosteroid-binding globulin (CBG), a glycoprotein specifically carrying cortisol in blood plasma, has been mapped. CBG is an important factor influencing bioavailability of the hormone, as it has been shown in humans that differences in CBG levels are a major determinant of differences in plasma cortisol levels. Therefore, the *Cbg* gene is an interesting positional and functional candidate gene to explain QTL influences on plasma cortisol levels. Indeed, comparison of gene sequences in Large White and Meishan pigs revealed several polymorphisms influencing CBG levels and function.

Corticosteroid Hormone Receptors

Two receptors (mineralocorticoid receptor [MR] and glucocorticoid receptor [GR]) mediate the biological effects of corticosteroid hormones. They act as transcription factors to increase or decrease the expression of target genes. The efficiency of corticosteroid hormone receptors is a major site of genetic variation, but few data are available in farm animals.

Functional Consequences of Genetic Variability

Physiopathological consequences of genetic variations in HPA axis activity reflect the wide range of corticosteroid hormone functions. Most data are related to growth and carcass composition. Indeed, glucocorticoid hormones influence feeding behavior; they also exert catabolic effects in peripheral tissues and anabolic effects in the liver so that they reduce growth rate and promote the accumulation of fat at the expense of proteins. In pigs, breeds with a higher body fat content such as Duroc and Meishan also produce more cortisol that lean breeds such as Large White and Landrace. In a segregating population (F2) of Large White × Duroc pigs, the fat content of the carcass was positively correlated with urinary levels of cortisol measured in the bladder after slaughter. In other studies in pigs, the magnitude of the adrenal response to ACTH – the main mechanism of genetic variability in HPA axis activity – was shown to be negatively correlated with body weight and growth rate. In sheep and turkeys, selection for leanness is accompanied by a reduction of HPA axis reactivity. Conversely, selection for a reduced adrenal response to cold stress in turkeys also increased body weight and egg production in turkeys, and growth rate was also inversely related to cortisol levels in divergently selected lines of rainbow trout.

Glucocorticoid hormones are also potent modulators of the immune system, and data obtained in chickens illustrate the consequence of genetic variation in HPA axis activity/reactivity on resistance to parasites or infectious diseases.

Perspectives

Current research in molecular genetics aims at the identification of gene polymorphisms responsible for individual phenotypic variation. For instance, there are documented mutations in the *Cbg* gene modifying its functional properties and associated with variable carcass fat content and meat quality of pigs. A single nucleotide polymorphism in the CRH gene was found to influence rib-eye area and carcass weight in beef cattle. In the future, it should be possible to optimize the functioning of the HPA axis by genetic selection based on molecular polymorphisms. When considering growth rate and carcass fat content, a low level of cortisol production should be favorable in the context of modern breeding for meat production. However, the picture is much less clear when considering the influence of HPA axis on other phenotypes. For instance, a lower cortisol response to social stress in poultry can either increase or decrease resistance depending on the infectious agent, and recently it was shown that plasma cortisol levels measured at birth are the best predictor of the genetic merit for piglet survival, with highest levels increasing survival. Further research will be necessary to better define the optimal activity of the HPA axis and to refine the molecular tools for farm animal selection.

See also the Following Articles

Adrenal Cortex; Comparative Anatomy and Physiology; Corticosteroid Receptors; Corticosteroid-Binding Globulin (Transcortin); Hypothalamic-Pituitary-Adrenal; Obesity, Stress and; Genetic Polymorphisms in Stress Response.

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