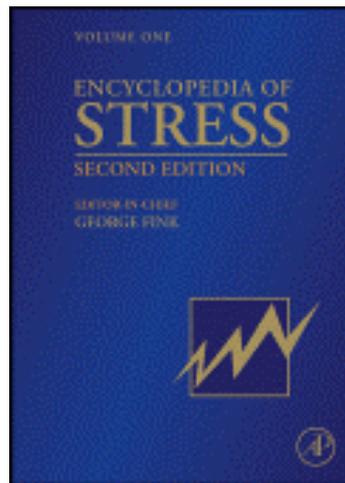


Provided for non-commercial research and educational use.
Not for reproduction, distribution or commercial use.

This article was originally published in the *Encyclopedia of Stress Second Edition*, published by Elsevier, and the attached copy is provided by Elsevier for the author's benefit and for the benefit of the author's institution, for non-commercial research and educational use including without limitation use in instruction at your institution,



sending it to specific colleagues who you know, and providing a copy to your institution's administrator.

All other uses, reproduction and distribution, including without limitation commercial reprints, selling or licensing copies or access, or posting on open internet sites, your personal or institution's website or repository, are prohibited. For exceptions, permission may be sought for such use through Elsevier's permissions site at:

<http://www.elsevier.com/locate/permissionusematerial>

Mormède P (2007), Strain Differences in Stress Response in Rodents. In: George Fink, (Editor-in-Chief) *Encyclopedia of Stress, Second Edition*, volume 3, pp. 585-586. Oxford: Academic Press.

Strain Differences in Stress Response in Rodents

P Mormède

INRA – Université Victor Segalen, Bordeaux, France

© 2007 Elsevier Inc. All rights reserved.

Strain Differences

Sources of Genetic Variability

Systems Genetics and Genetic Reference Populations

Glossary

<i>Inbred</i>	Obtained by continuous breeding of closely related individuals so as to preserve desirable traits in a stock.
<i>Inbred strain</i>	A strain of organisms that has been maintained by sibling (sister × brother) mating for 20 or more consecutive generations. Except for the sex differences, mice of an inbred strain are as genetically alike as possible, being homozygous at virtually all of their loci.
<i>Isogenic</i>	Genetically identical (except for sex); coming from the same individual or from the same inbred strain.
<i>Intercross</i>	A cross between two animals that have the same heterozygous genotype at designated loci; for example, between sibling F1 hybrids that were derived from an outcross between two inbred strains.
<i>Quantitative trait</i>	A phenotype that is influenced by multiple genes. Its variation is therefore continuous (skin color, weight, etc.).
<i>Quantitative trait locus (QTL)</i>	A polymorphic site on a chromosome containing alleles that differentially influence the expression of a quantitative trait.
<i>Recombinant inbred (RI) strains</i>	Strains constructed by crossing two inbred strains to produce an F1 generation, followed by 20 or more consecutive generations of brother × sister mating. However, the F1 generation may be produced in other ways, such as crossing mice of either existing RI strains, advanced intercross lines, or multiple inbred strains (e.g., an eight-way cross).
<i>Systems genetics</i>	A method for integrating across scales of organization using genetic reference populations. It summarizes results on molecular networks (gene expression data) associated with single-nucleotide polymorphisms SNPs and structural and functional variations.

Strain Differences

Inbred strains of mice and rats are invaluable animal resources for studying the genetic bases of phenotypic variation. They have been obtained through brother-sister mating for more than 20 generations, so all individuals have the same genome (isogenic) and each individual is homozygous at each locus. In a given environment, strain differences result from differences at the genome level.

Large variations in hypothalamic-pituitary-adrenal (HPA) axis activity have been described among inbred strains of rats and mice. Many of these studies are related to the pathophysiology of immune diseases, in which the HPA axis could play a critical role together with immune mechanisms. The Fischer 344 (F344) and Lewis rat strains particularly were studied in this respect, the Lewis female rats bearing an HPA axis that is less reactive to most stimuli and being more sensitive to induced autoimmune diseases such as streptococcal cell wall-induced arthritis or experimental allergic encephalitis. The sensitivity of the Lewis strain can be restored by the removal of the adrenal glands or by treatment with a glucocorticoid antagonist, and F344 rats become resistant when treated with glucocorticoid hormones. They are also studied in relation with the metabolic effects of corticosteroid hormones in the context of nutrition, obesity, and cardiovascular diseases.

Sources of Genetic Variability

It is not easy to detect the primary change(s) responsible for the functional variations of the HPA axis because phenotypic differences may be multiple and the components of the HPA axis interact strongly with numerous facilitation and feedback mechanisms at every level. For instance, when compared to F344 rats, the inbred brown Norway (BN) rats display a number of differences in their HPA axis function, with a different diurnal pattern of plasma corticosterone levels, a faster recovery after restraint stress, an adrenal gland of larger size but less reactive to adrenocorticotrophic hormone (ACTH), and mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) hypersensitive to their ligands.

Two main strategies are available for exploring the molecular bases of genetic variation. The detailed exploration of phenotypic differences may suggest candidate mechanisms and/or genes to analyze. For

instance, the comparison of BN and F344 rat strains suggested that the MR is a major source of genetic variability. Therefore, the gene encoding MR (named Nr3c2) was cloned in the two strains and sequenced, revealing in the BN strain a mutation in the coding region with an amino acid change in the protein (Y73C) that increases the transactivating properties of MR agonists.

Another approach, known as quantitative trait loci (QTL) analysis, is based on the association between polymorphic anonymous markers and the phenotypic value of the trait under study in a segregating population (such as F2 or backcross). In this approach, there is no need for any assumption about the gene(s) involved. In the case of the BN/F344 comparison, a QTL analysis confirmed the linkage between the mutation in the Nr3c2 gene and several MR-related phenotypes and disclosed several other loci contributing to phenotypic variability of MR- and GR-related phenotypes. Another study in a BN \times Wistar Kyoto hyperactive (WKHA) intercross revealed the contribution of a locus on chromosome 2 influencing poststress levels of renin and aldosterone. In this locus the angiotensin receptor 1b was mapped, which is responsible for angiotensin II (Ang II) effects on aldosterone secretion, and, indeed, differences were found in the response of adrenocortical cell to Ang II stimulation *in vitro*. This example illustrates the power of the QTL approach to reveal candidate genes possibly involved in phenotypic variation, as well as the multiplicity of mechanisms underlying genetic variation in corticosteroid hormone secretion and action.

Systems Genetics and Genetic Reference Populations

An extension of this QTL approach is the use of recombinant inbred (RI) strains, which are constructed by crossing two inbred strains to produce an F1 generation, followed by 20 or more consecutive generations of brother–sister mating. From a single F1 population, as many strains as possible can be derived. Each strain contains a unique, approximately equal proportion of genetic contributions from the two progenitor inbred strains. Instead of having a single individual for each genetic combination, as in an F2 population, each strain represents an unlimited number of animals with the same genotype, so the phenotype can be measured with more accuracy (in several animals instead of a single F2 animal) and different phenotypes measured across studies are cumulative and can be compared. Furthermore, precise genotyping of the strains with sequence-derived single

nucleotide polymorphisms allows precise QTL mapping. For instance the most used set of recombinant inbred strains with approximately 80 strains has been obtained from the C57BL/6 and DBA/2 mouse strains, and much larger sets (up to 1000 strains) are under construction. All data about these strains are integrated in a unique database named WebQTL that allows a large range of data mining from genetic correlation across multiple traits and QTL analysis. As an example, plasma corticosterone levels after an injection of saline (which can be considered as a mild stressor) was studied in 19 strains. In the WebQTL database of published phenotypes, genetic correlations are found between these levels and a number of phenotypes related to neuroanatomical and neurofunctional measures, response to drugs of abuse, and immune and inflammatory processes. This can be also correlated with gene expression data in different tissues. Therefore, these genetic reference populations allow a systems genetics approach that integrates all these data from diverse sources to explore genetic variation in HPA axis and in its target organs as a complex functional system.

See Also the Following Articles

Corticosteroid Receptors; Hypothalamic–Pituitary–Adrenal; Genetic Variation of HPA Axis Activity and Function in Farm Animals; Genetic Testing and Stress.

Further Reading

- Chesler, E. J., Lu, L., Wang, J., et al. (2004). WebQTL: rapid exploratory analysis of gene expression and genetic networks for brain and behavior. *Nature Neuroscience* 7, 485–486.
- Churchill, G. A., Airey, D. C., Allayee, H., et al. (2004). The Collaborative Cross, a community resource for the genetic analysis of complex traits. *Nature Genetics* 36, 1133–1137.
- Marissal-Arvy, N., Lombes, M., Petterson, J., et al. (2004). Gain of function mutation in the mineralocorticoid receptor of the Brown Norway rat. *Journal of Biological Chemistry* 279, 39232–39239.
- Mormède, P., Courvoisier, H., Ramos, A., et al. (2002). Molecular genetic approaches to investigate individual variations in behavioral and neuroendocrine stress responses. *Psychoneuroendocrinology* 27, 563–583.
- Peirce, J. L., Lu, L., Gu, J., et al. (2004). A new set of BXD recombinant inbred lines from advanced intercross populations in mice. *BMC Genetics* 5, 7–8.

Relevant Websites

Jackson Laboratory. www.jax.org.
WebQTL. www.genenetwork.org.