Multi-author Review

Genetic models in brain and behavior research, Part II

Progress report

P. Driscoll

Laboratorium für vergleichende Physiologie und Verhaltensbiologie, Turnerstrasse 1, ETH-Zentrum, CH-8092 Zürich (Switzerland)

Key words. Genetic variability; neurological mutant; cerebral laterality; alcohol consumption; alcohol sensitivity; hippocampus; inbred mice; selected rats and mice.

The use of the term 'progress report', as the title of the introduction to Part II of the multi-author review 'Genetic models in brain and behavior research', is not meant to imply that the reviews contained herein are more advanced than the reviews which comprised Part I (which, of course, covered other subjects[2, 5, 6, 9]), but to indicate that further progress has indeed been made in this field within the 15 months separating the two parts. In addition to this series, several supplements and 'special issues' of journals have appeared, as well as a number of individual articles which, coincidentally, have approached precisely two of the points stressed in the beginning of the introduction to Part I[3], those being the steadily increasing awareness of the importance of genetic factors in many clinical entities, and an expressed, personal desire for the construction of bibliographies of the many strains and stocks of rats and mice which are available to researchers.

In regard to the first point, it has been possible to observe a substantial increase in the number of articles related to the genetics of alcoholism, diabetes, hypertension, epilepsy and, in particular, to discover that a database of genetically-determined neurological conditions has been established, which already covers 1300 conditions with 3400 references[1]. Many of these entities are already represented by suitable, genetic animal models. At the same time (second point), investigators at the National Institute of Aging (USA) have produced a comprehensive bibliography of the nine mouse, and four rat genotypes which are obtainable from their colonies; one which will, in addition, be periodically updated and reproduced[7]. It may be hoped that more animal suppliers, especially those dealing with such genetically qualitative varieties, will follow suit.

As in Part I of the present series, the reviews which make up Part II deal with specific aspects of selective breeding and/or genetic comparisons in rats and mice. The paper by Carlson and Glick demonstrates that cerebral laterality is already well-documented in rodents, based on morphological, chemical and behavioral evidence. Furthermore, these interindividual differences have been shown to be associated with individual differences in spatial behavior, stress reactivity and pathology, and drug sensitivity. Sinclair et al. describe the history of one of the earlier examples of selective breeding: rats which voluntarily consume large quantities of alcohol vs rats which tend to avoid the consumption of alcohol. In addition to being used to study the role of genetic factors in alcohol consumption, which have long become well-established in the human literature[4, 8, 10–12], these lines of rats have been used to determine various behavioral, metabolic and neurochemical correlates of differential alcohol intake.

The paper by Wahlsten is also historic in nature, and describes the inheritance of a small or absent corpus callosum in mice; a spontaneous mutation which has been extended through recombinant inbreeding. Many other valuable mutations, mirroring human conditions, have occurred in mice (some of which are briefly mentioned by Wahlsten), but they will probably be impossible to cover in this series, unless it exceeds the four Parts which have been planned! The ongoing saga of the C57BL/6 and DBA/2 mouse strains[3, 5], however, has been continued by Van Abeelen, who shows how their behavioral differences may be used to advantage for exploring peptidergic, cholinergic and GABAergic neurotransmission in the hippocampus. Also using mice, Phillips et al. describe how selective breeding has been used to develop a number of strains differing in their sensitivity to ethanol. These genetic models for sensitivity to the hypnotic, thermoregulatory, excitatory and dependence-producing effects of alcohol have been extensively studied in order to determine the bases for their genetic differences, and to investigate the neurochemical and neurophysiological bases for ethanol's actions.

Finally, Lipp et al., expanding on an idea which goes back 200 years, illustrate a procedure for identifying relationships between brain and behavior which, in comparison to the classical lesion approach, has the advantages of being non-invasive and of focusing automatically upon those brain traits which are used by natural selection to shape the behavior of animal populations. The

following statement from that paper probably provides the most appropriate conclusion to this introduction: 'Concentration on genetic variability is not a matter of ideology but of practicality: a genetic difference is, by definition, resistant to masking influences due to plasticity or environmental factors and, thereby, more convenient to work with'.

1 Baraitser, M., Tomiwa, K., Wilson, J., and Winter, R., A database of genetically determined neurological conditions for clinicians. J. Neurol. Neurosurg. Psychiat. *52* (1989) 106–107.
2 Blizard, D. A., The locus ceruleus: a possible neural focus for genetic differences in emotionality. Experientia *44* (1988) 491–495.
3 Driscoll, P., Genetic models in brain and behavior research, Part I: Introduction. Experientia *44* (1988) 463–464.
4 Finn, P. R., and Pihl, R. O., Men at high risk for alcoholism: the effect of alcohol on cardiovascular response to unavoidable shock. J. abnorm. Psychol. *96* (1987) 230–236.
5 Frischknecht, H. R., Siegfried, B., and Waser, P. G., Opioids and behavior: genetic aspects. Experientia *44* (1988) 473–481.
6 Gentsch, C., Lichtsteiner, M., and Feer, H., Genetic and environmental influences on behavioral and neurochemical aspects of emotionality in rats. Experientia *44* (1988) 482–490.
7 Hazzard, D. G., and Soban, J., Studies of aging using genetically defined rodents: a bibliography. Exp. Aging Res. *14* (1988) 59–81.
8 Heath, A. C., and Martin, N. G., Teenage alcohol use in the Australian twin register: genetic and social determinants of starting to drink. Alcoholism: Clin. Exp. Res. *12* (1988) 735–741.
9 Overstreet, D. H., Russell, R. W., Crocker, A. D., Gillin, J. C., and Janowsky, D. S., Genetic and pharmacological models of cholinergic supersensitivity and affective disorders. Experientia *44* (1988) 465–472.
10 Schuckit, M. A., Genetics and the risk for alcoholism. J. Am. med. Assoc. *253* (1985) 2614–2617.
11 Tarter, R. E., Alterman, A. I., and Edwards, K. L., Vulnerability to alcoholism in men: a behavior-genetic perspective. J. Stud. Alcohol *46* (1985) 329–356.
12 Topel, H., Biochemical basis of alcoholism: statements and hypotheses of present research. Alcohol *2* (1985) 711–788.

0014-4754/89/090787-02$1.50 + 0.20/0

Cerebral lateralization as a source of interindividual differences in behavior

J. N. Carlson and S. D. Glick

Department of Pharmacology and Toxicology, and Interdepartmental Neuroscience Training Program, Albany Medical College, 47 New Scotland Avenue, Albany (New York 12208, USA)

Summary. Cerebral laterality can no longer be considered an exclusively human trait, as over the last 15 years there has been an emergence of data to suggest that animal brains are also lateralized. Morphologic, chemical and behavioral indices of brain asymmetry in the rodent have been reported, and it is suggested that variations in the magnitude and direction of these indices are determined by a complex interaction of genetic, hormonal and experiential factors. Interindividual differences in cerebral laterality have been shown to covary with, or predict, individual differences in spatial behavior and stress reactivity, as well as susceptibility to stress pathology and drug sensitivity. Such findings suggest that it is possible to study individual differences in lateralized brain function through the use of animal models.
Key words. Brain asymmetry; rotational behavior; genetic models; testosterone; brain development; stress; strain differences; sexual dimorphism; hemispheric differences.

Introduction

Findings accumulated over the last 100 years have repeatedly demonstrated that the human brain is functionally and anatomically lateralized. It has been shown that the left hemisphere is dominant in the control of language and handedness[33,43] and the right hemisphere dominant for emotion[40,41] and affect[23]. Implicit in these accounts of human brain laterality has been the assumption that, to some degree, individual differences in behavioral function could be accounted for by variation in the degree of such laterality. The tenability of such an assumption has been reviewed by others[23,42,93]. Until relatively recently, it had been assumed that cerebral lateralization of function is a distinctly human trait, e.g. Levy[74]. Over the past 15 years, however, findings have accumulated to suggest that cerebral lateralization of function is an evolutionary principle and not simply one indigenous to humans. Such brain asymmetries have been reported in species that range from songbirds[3,79] to non-human primates[71,72]. These findings have presented the opportunity to determine experimentally, using animal models, the degree to which individual differences in brain laterality may covary with, or determine, individual differences in behavioral functions.

Research conducted in this laboratory, and in others, has established that normal rats have functional and neurochemical asymmetries in several brain regions, and that wide individual differences exist on these measures. Much of this work has focused on the dopamine-containing nigrostriatal pathways: striatal asymmetries in dopamine levels, dopamine metabolites, dopamine release and dopamine uptake have been functionally related to rats' circling or rotational behavior, occurring either spontaneously at night or in response to drugs (e.g., d-amphetamine) during the day. Other work has focused