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Introduction to Special Issue

Molecular Genetic Approaches to Mammalian Brain and Behavior: An Introduction

Stephen C. Maxson[1]

Two of the goals of behavior genetics have been to identify individual genes with effects on brain and behavior and to determine the mechanism(s) for effects of individual genes on brain and behavior. With classical genetics, this would have consisted of identifying a gene by mapping it to a chromosome and of determining the pathways for its effects, tracing back from behavior or brain to the gene. Molecular genetics brings other approaches to these issues. Findings with molecular methods also lead to hypotheses with regard to mechanisms for effects of individual genes on brain or behavior. In this issue examples of molecular genetic approaches are described for perceptual (color vision and olfaction), motivational (circadian rhythms and sexual behaviors), learning and memory, and pathological (alcohol-related and schizophrenia) aspects of mammalian behavior.

KEY WORDS: Molecular genetics; mammalian; brain; behavior.

INTRODUCTION

Hall (1953) proposed that the objectives of behavior genetics are to determine (1) whether a behavior is heritable, (2) the number of genes segregating for the behavior, (3) the chromosomal location of each of these genes, and (4) the mechanism for effect of the gene(s) on the behavior. The first goal has been successfully achieved for many mammalian behaviors (Plomin *et al.*, 1990). This was accomplished, for the most part, with the tools of classical (quantitative and Mendelian) genetics. Considerable progress is being made for each of the other goals in the genetics of mammalian behaviors. To a large degree, this is due to development of molecular genetics, which began with the description in 1953 of the structure of DNA and of its relevance to gene replication, mutation, and function.

Molecular genetics is contributing greatly to chromosome mapping of genes for complex traits, such as mammalian brain and behavior, by the development of numerous markers, such as restriction fragment length polymorphisms (RFLPs) and simple sequence length polymorphisms (SSLPs). For example, there are at least 4006 SSLPs spaced about 0.35 cM apart for the mouse genome and at least 2066 SSLPs spaced about 2.9 cM apart for the human genome. Both association (Crabbe *et al.*, 1994) and linkage analyses (Ghosh and Todd, 1991) are being used to map genes for complex traits, including behaviors, of mammals. The mapped location of these genes may suggest that known genes are positional candidates or may lead to positional cloning of candidate genes. However, molecular genetic approaches can directly identify genes for complex traits prior to their chromosomal mapping and can contribute directly to determining the mechanisms for effects of these genes. These may also contribute to theories at the behavioral level.

Molecular genetics now provides two techniques for identifying and testing the functions of a gene. If a gene has been cloned and sequenced, induced mutants can be made for it. These may be either insertional mutants or knockout mutants. In this issue, the knockout mutant approach and its application to learning and memory are described by Wehner *et al.* Knockout mutants are described for α-calcium/calmodulin kinase II, protein kinase C, tyrosine kinase, and c-*fos*. Knockout mutants of

[1] Biobehavioral Sciences Graduate Degree Program, Department of Psychology, The University of Connecticut, Storrs, Connecticut 06269-4154.

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dopamine receptors, serotonin receptors, and the estrogen receptor are also being used in other behavioral research. In addition, two approaches are being developed for determining the tissue and temporal actions of the gene for its biological or behavioral effects. These are induced inactivation of the gene using controlled expression of Cre recombinase (Kuhn *et al.*, 1995) and antibiotic-induced expression of a transgene in its knockout (Gossen *et al.*, 1995). Also, if a gene is cloned and sequenced, antisense DNA can be used to block translation of its mRNA. The antisense DNA can be injected into a tissue, such as brain, at any time. This technique is described in this special issue by Ogawa and Pfaff for the progesterone receptor in relation to reproductive behaviors. Antisense DNA has also been used for neuropeptides, neurotransmitter receptors, transcription factors, and other genes (Hunter *et al.*, 1995). Molecular genetics brings not only new techniques to the study of the genetics of mammalian brain and behavior but also new concepts. Two of these are themes in several articles of this special issue.

The first conceptual theme is existence of multigene families, especially for sensory, hormonal, and neurotransmitter receptors (Schofield *et al.*, 1990). For neurotransmitter receptors, highly related but functionally distinct subtypes exist. This subtype diversity for proteins of the $GABA_A$ receptor may be involved, as discussed by Buck in this special issue, in the behavioral response to alcohol and the dopamine receptors may be involved, as discussed by Ginsburg *et al.* in this issue, in the taxonomy of schizophrenia. Multigene families and receptor diversity are also involved in color vision as discussed by Deeb and Motulsky and in olfaction as discussed by Breer *et al.* in this special issue.

The second conceptual theme is that experience via hormonal or neurotransmitter action can regulate gene expression (Morgan and Curran, 1989). This has been seen as a renaissance of the nucleus in neurobiology. For example, estrogens regulate the transcription of the neuropeptide cholecytokinin in neurons of the medial nucleus of the amygdala of the rat (Simerly, 1990); this may play a role in hormonal modulation of olfactory information. Also, in this special issue, Sagrillo *et al.* show that GnRH expression is regulated by action of neurotransmitters rather than hormones. Some of the effects of neurotransmitters on gene expression involve immediate early genes, such as c-*fos*. Immediate early genes code for transcription factors which, in turn, regulate expression of other genes. Two articles in this special issue consider the role of immediate early genes in effects of experience on behavior. These are by Kornhauser *et al.* on light regulation of expression of immediate early genes in the suprachiasmatic nucleus, which may be involved in setting the circadian clock, and by Dragunow on the role of glutaminergic and cholinergic regulation of immediate early genes of the hippocampus, which may be involved in long-term potentiation and learning.

Molecular genetics also can contribute to our understanding of brain and behavior functions. It is for this reason that each article relates the molecular genetic research to a specific aspect of behavior. Thus, there are articles on perceptions (color vision and olfaction), motivations (biological rhythms and reproductive behaviors), learning and memory, and psychopathologies. For each, molecular genetics not only is a way to find and characterize the genes but also stimulates new questions and hypotheses about the behaviors.

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