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Gene–environment interactions and construct validity in preclinical models of psychiatric disorders

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ABSTRACT

The contributions of genetic risk factors to susceptibility for brain disorders are often so closely intertwined with environmental factors that studying genes in isolation cannot provide the full picture of pathogenesis. With recent advances in our understanding of psychiatric genetics and environmental modifiers we are now in a position to develop more accurate animal models of psychiatric disorders which exemplify the complex interaction of genes and environment. Here, we consider some of the insights that have emerged from studying the relationship between defined genetic alterations and environmental factors in rodent models. A key issue in such animal models is the optimization of construct validity, at both genetic and environmental levels. Standard housing of laboratory mice and rats generally includes *ad libitum* food access and limited opportunity for physical exercise, leading to metabolic dysfunction under control conditions, and thus reducing validity of animal models with respect to clinical populations. A related issue, of specific relevance to neuroscientists, is that most standard-housed rodents have limited opportunity for sensory and cognitive stimulation, which in turn provides reduced incentive for complex motor activity. Decades of research using environmental enrichment has demonstrated beneficial effects on brain and behavior in both wild-type and genetically modified rodent models, relative to standard-housed littermate controls. One interpretation of such studies is that environmentally enriched animals more closely approximate average human levels of cognitive and sensorimotor stimulation, whereas the standard housing currently used in most laboratories models a more sedentary state of reduced mental and physical activity and abnormal stress levels. The use of such standard housing as a single environmental variable may limit the capacity for preclinical models to translate into successful clinical trials. Therefore, there is a need to optimize 'environmental construct validity' in animal models, while maintaining comparability between laboratories, so as to ensure optimal scientific and medical outcomes. Utilizing more sophisticated models to elucidate the relative contributions of genetic and environmental factors will allow for improved construct, face and predictive validity, thus facilitating the identification of novel therapeutic targets.

1. Introduction

Neuroscience and biomedical research have reached exciting stages, where the power of genetic, molecular, cellular and systems technologies has facilitated the generation of many new animal models that can be investigated using integrative approaches. The vast majority of animal models involve laboratory mice or rats, due to their relevance to human genetics, physiology and anatomy, as well as technical, temporal, financial and ethical constraints. It is often the case that successful preclinical results in a laboratory mouse or rat model are taken directly into clinical trials. However, the extent to which individual animal models exhibit construct validity for the particular disorder they are purported to model is highly variable. In this article we will discuss genetic and environmental factors which impact on the validity of preclinical models of psychiatric disorders.

2. Construct, face and predictive validity in animal models

When the stated aim of a research study or program is to model a human disorder, or endophenotype thereof, the animal models used can be assessed according to specific aspects of validity. Construct validity refers to the accuracy of the model with respect to the specific human disorder being studied. Thus, in a disorder such as Huntington's disease (HD), for example, a key requirement is that the human gene mutation (a CAG repeat expansion in the *huntingtin* gene) be expressed in the animal model. However, aspects of construct validity pertaining to environmental

Abbreviations: COMT, catechol-O-methyltransferase; THC, Delta-9-tetrahydrocannabinol; HD, Huntington's disease; SNPs, single nucleotide polymorphisms; GWA, genome-wide association; TRPs, tandem repeat polymorphisms; SSRIs, selective serotonin reuptake inhibitors.

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factors are generally given less attention. The inclusion of environmental factors in models of psychiatric disorders is critical as interactions between the environment and genetic predisposition underlie aetiology and thus constitute a key aspect of the disorder being modeled and should not be ignored. This common oversight, and its implications for limiting translatability of preclinical studies, are discussed in detail below.

Face validity refers to the extent to which the animal model exhibits behavioral, cellular and molecular characteristics which reflect the human disorder being modeled. For example, ideally an animal model of schizophrenia would present with positive, negative and cognitive endophenotypes reflecting clinical symptoms, as well as cellular and molecular changes in key brain areas including the neocortex and hippocampus.

Predictive validity can only currently be assessed for those models where an at least partly effective clinical treatment is available. Thus, an animal model of depression exhibiting endophenotypes which are corrected to control levels by chronic administration of a clinically effective antidepressant drug is said to exhibit predictive validity. Similarly, the predictive validity of schizophrenia models is assessed using commonly prescribed antipsychotic drugs. While the modeling of complex cognitive and behavioral endophenotypes of such psychiatric disorders in laboratory animals is challenging, the ability to test predictive validity using existing drugs does provide one advantage, relative to the modeling of other disorders (e.g. Alzheimer's disease) for which no treatment is currently available.

3. Parsing construct validity in animal models: sex, genes and environment

3.1. Sex: a taboo subject in rodent model research?

The majority of published studies on rodent models of psychiatric disorders use only male animals. The most cited reason is that females have increased variability due to estrous cycle and associated hormonal fluctuations (Meziane et al., 2007). The reality is that most diseases (with rare exceptions affecting X/Y chromosomes or the sex organs) affect both men and women. That said, many diseases exhibit sexual dimorphism. For example, the cognitive symptoms in schizophrenia and attention deficit hyperactivity disorder are more pronounced in males (Gershon, 2002; Halbreich and Kahn, 2003) and a higher prevalence of stress-related disorders such as depression and anxiety has been observed in women (Frackiewicz et al., 2000; Sandford et al., 2000). While sexually dimorphic biology may partly explain these epidemiological examples, there is also a potential role for sexual dimorphism in the way males and females engage with, and are affected by, their environments, which could also influence the expression of psychiatric symptoms (Accortt et al., 2008; Rose and Rudolph, 2006). Furthermore, males and females may respond differently to the same treatment due to sexually dimorphic pharmacokinetics, pharmacodynamics or other factors (reviewed by Gartlehner et al., 2010). For all of these reasons it is imperative that, for disorders which occur in both sexes, preclinical trials are conducted on both male and female animals.

3.2. Genes: accurate modeling of causative mutations/polymorphisms and appropriate control of background strain

All human brain disorders, even those with high environmental loads such as stroke, can be affected by genetic factors. The majority of biomedical studies in animals are conducted on a small number of laboratory mouse and rat strains. Laboratory mice are usually derived from inbred strains (e.g. C57BL/6) and therefore exhibit little or no genetic variability, in contrast to the enormous genetic heterogeneity exhibited by a typical human cohort. While some common laboratory rat strains used are outbred (e.g. Sprague Dawley), the genetic variance is limited.

For each particular disorder, genetic construct validity is determined by how closely the gene mutation(s) in the animals match those of the disease-associated mutations/polymorphisms. At present, while monogenic diseases can be genetically modeled in rodents (usually transgenic, knock-in or knock-out mouse lines) it is extremely difficult to accurately model complex polygenic disorders (e.g. schizophrenia, autism and depression). However, relevant insights can be provided by mouse models involving rare monogenic forms of autism (e.g. neuroligin-3 and -4), de novo chromosomal abnormalities in schizophrenia (e.g. 22q11.2) and a monogenic disease associated with high rates of depression (e.g. HD).

Even in the case of monogenic diseases, a mutant mouse model bred onto different background genetic strains can exhibit strikingly different phenotypes, suggesting complex gene–gene interactions and genetic modifier effects. This has been observed in mice containing a mutation in the neuroligin-3 gene, a model with relevance to autism. Mutants bred onto a mixed genetic background (C57Bl/6xSV129) show impairments in social behavior, however this phenotype was no longer present when mice were backcrossed to a pure genetic background (Chadman et al., 2008; Tabuchi et al., 2007). Despite these challenges, the biomedical research community has been focused on improving 'genetic construct validity' and utilizing the power of recent genomic technologies and genome-wide associations studies will continue to do so. It is the issue of 'environmental construct validity' that has received less attention, and may represent the greatest hurdle in achieving optimal translation from preclinical studies to clinical trials.

3.3. Gene×environment interactions: unmasking new phenotypes

Despite the recent breakthroughs in psychiatric genetics, it has proven difficult to directly link genotypes with distinct behaviors and to isolate candidate genes that contribute to specific behavioral impairments in affected individuals (Hanmer et al., 2010; Mackay and Anholt, 2007). Part of this difficulty stems from the polygenic nature of psychiatric disorders, and from the tendency of earlier research to focus on exploring a linear relationship between genes and behavior (Kas and Van Ree, 2004). When combined with environmental challenges certain genetic mutations can be either protective or pathogenic, depending on the nature of the environmental factor and the time of interaction. Thus, a focus on genetic construct validity alone has limited heuristic value due to the interdependent interactions between genetic and environmental factors that play key roles in the pathogenesis. Models incorporating both genetic and environmental factors can produce completely new phenotypes, previously undetected in unchallenged mutant mice or in wild-type animals exposed to an environmental manipulation. It is not possible to fully understand the action of genes on cognitive and behavioral disorders without consideration of the environment, and valid animal models should address both genetic and environmental variables in an integrated manner.

The gene–environment interaction approach reconciles the 'nature versus nurture' dichotomy (Caspi and Moffitt, 2006; Mackay and Anholt, 2007) and brings a new understanding that genes and environmental factors interact in interdependent ways (Canli and Lesch, 2007). The use of animal models based on identified genetic mutations and measureable environmental factors to study molecular mechanisms of gene–environment interplay has been recently discussed (Ayhan et al., 2009; Gray and Hannan, 2007). Animal models utilizing environmental manipulations that parallel the results of epidemiological studies in psychiatry have been critical to advancing our understanding of the biology of psychiatric conditions. However, it is the animal models incorporating genetic and environmental factors, as well as gene–environment interactions, that more accurately mimic etiologic factors and help to elucidate underlying pathogenic mechanisms. Previously unseen phenotypes