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Review

Mouse models of gene–environment interactions in schizophrenia

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ABSTRACT

Gene–environment interactions (GEIs) likely play significant roles in the pathogenesis of schizophrenia and underlie differences in pathological, behavioral, and clinical presentations of the disease. Findings from epidemiology and psychiatric genetics have assisted in the generation of animal models of GEI relevant to schizophrenia. These models may provide a foundation for elucidating the molecular, cellular, and circuitry mechanisms that mediate GEI in schizophrenia. Here we critically review current mouse models of GEI related to schizophrenia, describe directions for their improvement, and propose endophenotypes to provide a more tangible basis for molecular studies of pathways of GEI and facilitate the identification of novel therapeutic targets.

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Introduction

Genetic and environmental factors, as well as their interplay, contribute to individual differences in vulnerability to psychiatric disease (Kas et al., 2007; van Os et al., 2008). Gene–environment interplay is a term that encompasses several models (Kendler and Eaves, 1986; Rutter et al., 2006). These include altering gene expression by environmental factors via epigenetic mechanisms, additive interaction between genetic and environmental factors, gene–environment correlations or genetic control of exposure to the environment, and genetic control of sensitivity to the environment (Kendler and Eaves, 1986; Rutter, 2008; Rutter et al., 2006). Genetic moderation of individual susceptibility to the adverse or protective effects of the environment provides an explanation for most examples of what have been termed as genotype–environment interactions (GEIs) (Rutter et al., 2006). This review will focus on mouse models that mimic GEIs etiologically relevant to schizophrenia.

GEIs are difficult to assess in clinical studies (Heath et al., 2002; Uher, 2009). Animal models offer a means of elucidating the contribution of genes, environmental factors, and their interactions on pathogenesis

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of psychiatric disease (Rutter, 2002; Tecott, 2003). As technology has and continues to develop, a number of genetic models can be made to use in conjunction with environmental insults to look at GEI. However, the most useful models to study human disease should incorporate genetic changes and environmental components that are etiologically relevant (Ayhan et al., 2009; Caspi and Moffitt, 2006).

As schizophrenia and related disorders are increasingly considered as disorders that include etiologies associated with brain development, rodent models with manipulation in genes involved in neurodevelopment may be useful (Insel, 2011; Jaaro-Peled et al., 2009). In a similar vein, it is important to take developmental considerations into account when interpreting environmental effects that can be variable in different age groups. For schizophrenia, pre- and postnatal events that induce psychological stress seem to exacerbate symptoms in adulthood, infectious etiologies have predominantly been associated with prenatal exposure, and illicit use of drugs has been found to be relevant during early adolescence (Moffitt et al., 2005; Rutter, 2008).

We have also proposed that promising animal models of GEI would include etiologically relevant genetic and environmental risk factors that would have a strong functional impact and converge on common signaling pathways (Ayhan et al., 2009). Thus, we will overview mouse models that combine genetic variations with psychological stressors (Bethus et al., 2005; Koenig, 2006; Markham and Koenig, 2011), immune activation (Brown et al., 2004; Patterson, 2007) and cannabis exposure (Caspi et al., 2005; Henquet et al., 2005, 2008). The present review will critically evaluate the weakness of the current approaches and will suggest possible new directions in the development of GEI models with a particular focus on endophenotypic measures that are thought to be instrumental for mechanistic studies, more readily translatable to human conditions, and targetable by therapeutics (Battaglia et al., 2008).

Endophenotypes in animal models for GEI in schizophrenia

As it is impossible to faithfully create the key features of schizophrenia such as hallucinations and delusions in animals, a more tractable and promising approach that has been gaining attention is to model brain circuitry, cellular, and molecular alterations associated with the disease. Such alterations can be broadly termed as endophenotypes (Amann et al., 2010). In the context of GEI animal models, the main advantage of endophenotypes is that such abnormalities can be objectively measured in patients and faithfully replicated in animals to help decipher the underlying mechanisms of GEI. Here, we briefly overview several endophenotypes that are relevant to schizophrenia and may be utilized in basic studies of GEI.

Behavioral endophenotypes

Despite the obvious reservations about reproducing human emotion and cognition in animals, some behaviors are conserved in humans, primates, and rodents. Changes in some evolutionarily preserved behaviors are observed in patients and can be experimentally induced in animals, including hyperactivity, impaired pre-pulse inhibition (PPI) of the acoustic startle response, deficient social interaction, and cognitive deficits (Kas et al., 2007). Although these behavioral alterations are not specific to schizophrenia, their objectivity and reproducibility make them useful endophenotypes. For example, as PPI is diminished in patients with schizophrenia (Braff et al., 2001), testing for PPI impairment remains a critical component of any animal study of schizophrenia (Geyer, 2002; Powell et al., 2012; Swerdlow et al., 1992). Similarly, given that cognitive deficits are debilitating and the least treatable abnormalities in schizophrenia (Keefe, 2008; Reichenberg et al., 2006), there is a growing appreciation for developing more sophisticated tests to evaluate cognitive processes, including working memory and attention (Arguello and Gogos, 2006; Kellendonk et al., 2009). Behavioral endophenotypes have been widely used in animal models of major psychiatric diseases and animal models of GEI. Still, more work is needed to develop translatable and reproducible behavioral endophenotypes for negative symptoms and cognitive deficits of the disease (O'Tuathaigh et al., 2010).

Electrophysiological endophenotypes

Patients with schizophrenia display deficits in processing external stimuli from the environment (Barch and Ceaser, 2012; Rissling and Light, 2010; Silverstein and Keane, 2011). These deficits can be assessed with auditory event-related potential (ERP) methodology. Reductions in N100 or mismatch negativity, and changes in theta and gamma frequency have been proposed as electrophysiological endophenotypes relevant to schizophrenia (Ford et al., 2007; Thaker, 2008; van der Stelt and Belger, 2007). Such endophenotypes can now be successfully measured in animals (Amann et al., 2010; Ehrlichman et al., 2008, 2009). Abnormal functional inter-regional connectivity has also been implicated in the pathophysiology of schizophrenia (Schmitt et al., 2011; Uhlhaas, 2012). Newly developed tools enable us to study functional connectivity in laboratory animals. For example, reduced synchronization of neural activity between the hippocampus and the prefrontal cortex during a working memory task was found in a mouse model of the 22q11.2 deletion (Sigurdsson et al., 2010). Another electrophysiological method that is being developed to examine the pathophysiology of cognitive impairment is stimulus specific response potentiation. This tool can be used to assess long-lasting, experience dependent plasticity in the primary visual cortex of rodents (Cooke and Bear, 2012). These techniques are only beginning to be utilized in animal models of psychiatric disease but hold the significant promise of objectively evaluating effects of GEI at the circuitry level, particularly in combination with in vivo imaging.

Brain imaging endophenotypes

The introduction of neuroimaging has revolutionized brain research, providing significant insights into the pathophysiology of psychiatric diseases (Lancelot and Zimmer, 2010; Nenadic et al., 2012; Shepherd et al., 2012; Vyas et al., 2012). Adaptation of neuroimaging to rodents has enabled researches to observe in vivo longitudinal changes at the organ, cell, and molecular levels (Lancelot and Zimmer, 2010; Poole et al., 2011). Magnetic resonance imaging (MRI) has been used to assess volumetric changes in the lateral ventricles and brain regions in several animal models for schizophrenia (Denic et al., 2011; Dijkhuizen and Nicolay, 2003; Hikida et al., 2007; Pletnikov et al., 2008). The animal variant of positron emission tomography (PET), micro-PET, has been helpful in assessing neurochemical changes (e.g. receptor binding) that resemble PET findings in patients (Sossi and Ruth, 2005). The simultaneous use of MRI and micro-PET in rodent models of schizophrenia may provide valuable information on changes in receptor density and neurotransmitter and metabolite concentration due to specific genetic or environmental manipulations (Lancelot and Zimmer, 2010). The significant advantages of in vivo neuroimaging are longitudinal monitoring of the brain alterations of GEI and the treatment effects in the same animal. However, the cost of neuroimaging is high and likely deters wider use of this technology. Also, the low resolution of the images may make subtle changes difficult to assess, requiring the use of traditional histological methods.

Histological endophenotypes (GABA neuronal changes and spines)

Histological analysis provides insight into specific cell modifications (e.g. number or morphology) that still are unavailable with in vivo imaging. Decreased immunoreactivity of parvalbumin positive gamma-aminobutyric acid (GABA) interneurons in the cortex and hippocampus is commonly observed in postmortem brains of patients with schizophrenia (Gonzalez-Burgos and Lewis, 2008). This