Mutant models for genes associated with schizophrenia

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Abstract

Schizophrenia is a highly complex and heritable psychiatric disorder in which multiple genes and environmental factors interact to cause the schizophrenia phenotype. A new generation of molecular studies has yielded numerous candidate genes with a putative role in risk for schizophrenia, whereas other genes regulate putative pathophysiological mechanisms. Mutant mice having either deletion (knockout) or insertion (knockin/transgenesis) of schizophrenia risk genes now allow the functional role of these genes to be investigated. In the present mini-review, we outline the advantages and limitations of various approaches to phenotypic assessment of mutant mouse models, including ethologically based methods. Thereafter, we consider recent findings, with a particular focus on, first, dopaminergic and glutamatergic pathophysiological models and, secondly, putative roles for *DISC1* (disrupted in schizophrenia 1) and *NRG1* (neuregulin 1) as susceptibility genes for schizophrenia. Finally, we identify current challenges associated with the use of genetic mutant models and highlight their potential value for exploring gene–gene and gene–environment interactions in relation to schizophrenia.

Introduction

Schizophrenia is a multifaceted disorder characterized by a combination of positive, negative and cognitive symptoms that vary in composition and severity and by functional deficits that are associated with a variable outcome. Genetic epidemiological studies indicate a strong genetic component to the disorder, with a complex pattern of inheritance that is most consistent with a multi-locus basis, and a new generation of molecular studies has now yielded numerous candidate genes [1–4].

The ability to construct specific mutations at these loci in mice, by either deleting (knockout) or inserting (knockin/transgenesis) individual genes, provides a powerful means to investigate their functional roles and putative contributions to the pathobiology of schizophrenia; the construction of such mutants permits molecular specificity and, through conditional mutants, spatial and temporal overexpression of the gene in question [3,5–7].

Genes associated with schizophrenia can be divided into two categories: those regulating putative pathophysiological mechanisms and those associated clinically with risk for the disorder. Because of evidence and theoretical models implicating the neurotransmitters dopamine and glutamate in the pathobiology of schizophrenia [8,9], mutants relating to the first category typically involve these key neurotransmitters. Among the second category, mutants with disruption to two of the most consistently replicated genes [3,4], *DISC1* (disrupted-in-schizophrenia-1) and *NRG1* (neuregulin-1), have attracted particular attention.

Methods of phenotypic assessment

Phenotypic analysis of mice with targeted mutation of susceptibility genes provides a powerful means of identifying the functional roles of these genes and how they might contribute to the pathobiology of schizophrenia. A broad hierarchically based approach that screens the phenotype at multiple basic levels is important in determining the overall effect of the mutation in terms of general anatomy, physiology and behaviour; this is especially important when the context of the mutation is less clear and/or is not the subject of a hypothesis. A more targeted phenotypic approach focuses on specific and quantifiable measures deriving from some known or hypothesized role(s) of the gene in question and/or some sense of those phenotypes that indicate relelevance for the disorder at issue.

Endophenotypes, i.e. discrete, quantitative, genetically determined features that may be part of a complex illness but are not necessarily part of the clinical presentation [3], can aid the task of investigating causal relationships between susceptibility genes and the disorder. Phenotypic and endophenotypic analyses of mutants can be conducted at multiple levels, ranging from the examination of structural, cellular and physiological parameters that are more proximal to the genetic mutation to assessing fundamental effects on behaviour that are more distal to the mutation. Modelling the psychopathology of schizophrenia in the mouse, e.g. the positive symptoms of delusions and hallucinations, presents a possibly insurmountable challenge; however, certain measures, such as hyperresponsivity to novelty and hypersensitivity to

Key words: disrupted in schizophrenia 1 (DISC1), mutant model, neuregulin-1, pathophysiology, risk gene, schizophrenia.

Abbreviations used: COMT, catechol-O-methyltransferase; DISC1, disrupted in schizophrenia 1; NMDA, *N*-methyl-D-aspartate; NRG1, neuregulin 1; TM, transmembrane.

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psychostimulants, have been considered as correlates of these symptoms in rodents. Other behavioural traits, including sociability, motivational state and aspects of cognition, particularly working memory, are considered to be useful indices of the negative and cognitive symptoms of the disorder [5].

The advantages of an ethologically based approach to behavioural assessment have also been highlighted and discussed in the literature [7,10,11]; the underlying premise is that assessment of a particular aspect of behaviour in a 'naturalistic' setting (taking into consideration consummatory needs, social structure and hazards associated with the natural habitat) can be more incisive for identifying changes in disease-relevant neurocircuitry and reveal deficits that would not necessarily be apparent using more structured behavioural tasks.

Genetic models related to pathophysiological aspects of schizophrenia

Dopaminergic mechanisms

Deriving from antagonism of D_2 dopamine receptors being the only property common to all known antipsychotic drugs, the dopamine hypothesis of schizophrenia states that heightened transmission through D_2 receptors in subcortical brain regions is the basis of positive symptoms, whereas reduced transmission through D_1 receptors in cortical regions may contribute to negative symptoms and cognitive deficits; this proposition is now supported by a number of neuroimaging studies in patients [9].

D_2 receptor transgenics

Relationships between heightened dopaminergic transmission and a schizophrenia endophenotype have been investigated using conditional transgenics that overexpress striatal D_2 receptors in a site-specific and temporally controlled manner [12]. The phenotype was characterized by impaired prefrontal cortex-mediated working memory and reduced behavioural flexibility in a T-maze that persisted after the transgene was switched off, indicating that these effects occur as a result of secondary compensatory mechanisms and are not solely due to direct effects of D_2 receptor overexpression. Interestingly, striatal D_2 overexpression also altered dopamine turnover and D_1 receptor activation in prefrontal cortex, suggesting a basis for these cognitive deficits.

COMT (catechol-O-methyltransferase) knockouts and transgenics

COMT is an enzyme involved in the degradation of dopamine, particularly in prefrontal cortex where re-uptake mechanisms for dopamine are sparse; additionally, the locus of the *COMT* gene, 22q11.2, has been associated with risk of schizophrenia [4] and a *COMT* genotype has been associated with a cognitive endophenotype [13].

Heterozygous deletion, but not homozygous knockout, of *COMT* disrupted exploration of and habituation to a novel environment [14]. However, knockout, but not heterozygous deletion of *COMT* resulted in improved spatial learning and working memory [15,16], a finding that is consistent with clinical studies showing an association between the Met allele, which is characterized by reduced COMT-mediated degradation of dopamine, and enhanced prefrontal cortex-mediated cognition [13,17]. In our own studies [15], this phenotypic effect was sex-specific, being evident in male, but not in female, knockouts.

Transgenics overexpressing a human *COMT*-Val polymorphism, and therefore characterized by increased COMT activity, exhibited impaired working and recognition memory, deficits in attentional behaviour and attenuated sensitivity to stress and pain; impairment in working and recognition memory was ameliorated by amphetamine, confirming an involvement of dopamine in these cognitive effects [16].

Glutamatergic mechanisms

The glutamate [NMDA (*N*-methyl-D-aspartate)] receptor hypofunction hypothesis of schizophrenia is based largely on findings from pharmacological studies, whereby the NMDA receptor antagonists PCP (phenylcyclohexylpiperidine or phencyclidine) and ketamine induce both positive and negative symptoms in normal subjects and exacerbate these symptoms in patients, while indirect NMDA agonists can result in symptom improvement [18,19]; an NMDA receptor deficit in patients has been reported in SPECT (single-photon emission computed tomography) studies [20].

NMDA receptor 1 hypomorph

In support of the involvement of NMDA hypofunction in schizophrenia, mutants with 90% reduction in NMDA receptor 1 expression show behavioural abnormalities in adulthood, including increased motor activity and deficits in social and sexual behaviour [21]; importantly, these behavioural abnormalities were sensitive to amelioration by the antipsychotics haloperidol and clozapine, particularly for hyperactivity although less so for social deficits, indicating that NMDA and dopamine systems interact at some level in these phenotypic effects.

Genetic models of risk for schizophrenia

Among several genes now implicated in risk of schizophrenia [1–4], for the purpose of the present review, we will focus on two of the most topical and well-characterized mutant models: DISC1 and NRG1.

DISC1

The *DISC1* gene is located at the breakpoint of a balanced t(1;11) chromosomal translocation; in a Scottish sample, this mutation was found to segregate with mental illness, including schizophrenia, and this finding has been replicated subsequently in a variety of populations worldwide [22,23]. Although the precise functions of the *DISC1* gene remain

unclear, it is reported to be maximally expressed in the brain during development and interacts with numerous cytoskeletal proteins, including phosphodiesterase 4B, suggesting that it may have a role in neurite outgrowth, cell migration and cell signalling [24].

There are now several studies on DISC1 mutants. Mice of the commonly employed 129S6 Sv/Ev strain have been shown to carry a 25 bp deletion in exon 6 of the *Disc1* gene; alterations to the organization of newly formed and mature neurons and deficits in short-term plasticity may contribute to the working memory impairments reported in these mice [25,26]. Chemical mutagenesis of exon 2 of the *Disc1* gene resulted in impairment in prepulse inhibition and in latent inhibition, with enhanced locomotor responsivity to novelty that was reversed by antipsychotic treatment [27]. Transgenic mice expressing a dominant-negative form of *Disc1* under the CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II) promoter exhibited enhanced locomotor responsivity to novelty, with enlarged lateral ventricles at 6 weeks [28]. In a transgenic line with inducible expression of a DISC1 C-terminal fragment [29], early postnatal, but not adult, induction was associated with deficits in working memory and reduced sociability. An inducible transgenic line restricting expression of mutant DISC1 to the forebrain demonstrated hyperactivity in the open field, with reduced social investigation only in male mutants and impaired spatial working memory only in female mutants [30]. Given material gender differences in schizophrenia with respect to incidence, age at onset, response to treatment and long-term outcome, further exploration of the influence of sex on the phenotypic expression of susceptibility genes such as *DISC1* is warranted.

NRG1

The neuregulins are a family of signalling proteins that share a common EGF (epidermal growth factor)-like domain which interact with membrane-associated tyrosine kinases (ErbBs) to activate intracellular signalling pathways known to play an important role in various developmental processes [31,32]. *NRG1* was first identified as a potential schizophrenia susceptibility gene in an Icelandic study [33] and subsequent findings have sustained this association [4,34,35].

The majority of NRG1 proteins are synthesized with a TM (transmembrane) domain. Mutants with heterozygous deletion of the TM domain NRG1 exhibited hyperactivity when examined in anxiety- and exploration-related tasks [33,36–38], an effect that was reversed by the antipsychotic clozapine [33]. Adopting an ethologically based approach to behavioural analysis has proved to be of particular value in elucidating novel phenotypic effects [11]; application to TM domain NRG1 mutants revealed sex-specific effects on individual topographies of behaviour in the murine repertoire [36]. These mutants also exhibited a deficit in prepulse inhibition [33], selective impairment in social novelty preference [39] and altered patterns of social interaction in dyadic encounters [39,40].

Studies focusing on deletion of specific NRG1 isoforms have shown that type III NRG1 mutant mice display more pronounced deficits in prepulse inhibition than those exhibited by TM domain NRG1 mutants and also demonstrate impairment in working memory; however, the absence of any effect on aggression [41] suggests that TM-domain containing NRG1 isoforms other than type III are involved in the expression of this phenotype. Interestingly, neither type III NRG1 mutants [41] nor those with targeted disruption of type I/type II NRG1 (NRG1 isoforms containing an immunoglobulin-like domain) [42] induce the hyperactivity that is characteristic of TM-domain NRG1 mutants; this suggests that the effects of specific mutation of NRG1 isoforms on behavioural phenotype may be masked by the compensatory activity of other genes or environmental factors. Overall, a more comprehensive analysis of the phenotypic profiles of mutants for each of these and other NRG1 isoforms is required to illuminate further their relative importance for the pathogenesis of schizophrenia.

Opportunities and challenges

It is becoming increasingly recognized that mutant models, including those involving putative schizophrenia-related genes, are accompanied by a number of inherent limitations [11,43,44]. Despite their merits, it must be emphasized that mutation for a specific susceptibility gene is unlikely to give rise to a phenotype that encompasses all aspects of schizophrenia; such mutants should not be considered to model schizophrenia, but, rather, to model the functional roles of genes associated with risk of schizophrenia.

In addition, as such genetic mutations occur upstream from the cellular and physiological mechanisms that ultimately give rise to abnormal behaviour, they are inevitably subject to environmental influences and compensatory/adaptive effects initiated by homoeostatic processes during development; this buffering effect can involve alterations in the expression of other genes, i.e. epistasis. Such processes may introduce confounding effects that obscure the role of any single gene in the schizophrenia phenotype or an endophenotyope. Potential means of overcoming these issues include the use of conditional mutants or increasingly popular RNA interference technologies that allow region- and time-specific manipulation of a particular gene. Also, exploring the effects of multiple mutations of schizophrenia risk genes is likely to improve understanding of the schizophrenia phenotype and could open new avenues in the search for more effective therapies for this disorder.

Furthermore, the use of mutant models is complicated by the possibility that the pathogenic effect of one or more schizophrenia-related gene(s) is influenced not only by the presence of an environmental event, but also on the severity and timing of that event [45]. Examination of the effect of environmental manipulations on mutant phenotype at specific developmental stages would help define the trajectory, relative contribution of and interaction between genes and adverse environmental factors in emergence of the schizophrenia phenotype.

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