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Review

Closing the translational gap between mutant mouse models and the clinical reality of psychotic illness

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ABSTRACT

As animal models of psychotic illness become more refined, mutant mouse models have become increasingly prominent through their ability to inform on the structural, cellular and behavioural roles of genes associated with risk for psychosis via the phenotypic consequences of disruption of those genes. This review will consider recent advances in the field whereby mutant mouse models seek to reflect increasing knowledge of psychotic illness, focusing on four main themes. Firstly, recent GWAS and rare variant analyses have identified that disease-associated targets have not been previously implicated, thereby representing novel biological pathways in the illness, and this has implications for the modelling field. Secondly, the psychosis is disrespectful to conventional diagnostic boundaries, both clinically and in terms of pathobiology: it extends beyond schizophrenia to include several diagnostic categories and may be best captured in terms of psychopathological dimensions rather than/additional to such categories. Thirdly, a given risk gene (G) does not operate in isolation but, rather, appears to participate in complex interactions with environmental (E) risk factors, i.e. G × E interactions. Lastly, a given risk gene is likely to participate in complex, epistatic interactions with other risk genes, i.e. G × G interactions. Such studies constitute important steps in closing the translational gap between mutant mouse models and the clinical reality of psychotic illness.

Contents

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1. Introduction

Our understanding of schizophrenia is challenged by its complex life-course and multifactorial origins that involve contributions from diverse genetic, epigenetic and environmental factors (van Os and Kapur, 2009; Brown, 2011; Hall et al., 2014). A wealth of evidence now indicates that schizophrenia is a neurodevelopmental disorder characterised by high heritability, where the emergence of diagnostic psychotic symptoms represents an outcome of a pathobiological cascade that has its origins in the earliest stages of brain development (Rapoport et al., 2012; Waddington et al., 2012). While the precise nature of the genetic defect is still largely unknown, recent genome-wide association studies (GWAS) and rare mutation studies have provided new insights into the aetiology of this and related disorders, and hold out the prospect (as yet unrealised) of new directions for antipsychotic drug discovery (Winchester et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

In the face of such complexities, the past decade has seen a progressive reduction in investment in antipsychotic drug discovery; this is indicative of reprioritisation within the CNS pharma sector, and is considered to be largely attributable to high failure rates in clinical trials, incomplete understanding of disease mechanisms, and the absence of unequivocal treatment biomarkers (Muglia, 2011; Hyman, 2014; Agid et al., 2013). Our current understanding of schizophrenia is still lacking with respect to diagnostic pathobiology and strong causative genetic mutations (Del Pino et al., 2013). As a result, while investigations on the nature of psychotic illness continue to progress in an incremental fashion, it has yet to lead to major advances in the development of novel antipsychotic drugs. This current impasse vis-à-vis antipsychotic drug discovery may also reflect ongoing debate in the field as to current concepts of psychosis. Within this theoretical milieu resides the practical reality that both negative and cognitive symptoms, and their associated functional impairments, have proven resistant to both first- and second-generation antipsychotic drugs. This provides a yet greater imperative for both human and preclinical genetic studies to contribute to the development of new antipsychotics (Karam et al., 2010).

For preclinical studies to advance in their heuristic import, they must reflect these evolving concepts, with a particular focus on: (a) psychotic illness as a dimensional construct that involves several domains of psychopathology and dysfunction that are disrespectful to our current nosology; these intersect with a yet broader range of psychopathologies and dysfunctions that are associated with a broader range of neurodevelopmental disorders, such as autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), that are considered classically to reside outside the psychosis spectrum. (b) Increasing evidence for not only psychopathological but also genetic, epidemiological-environmental and pathobiological overlap between schizophrenia, bipolar disorder and other neuropsychiatric disorders in which psychosis can occur. (c) Psychotic illness not as a point of onset of a disorder but, rather, a stage in the trajectory of a disorder that is manifested throughout the lifespan: from the neurological and psychosocial/intellectual deficits of infancy, childhood and adolescence that are evident on a population basis, but are too subtle to be of diagnostic utility; through to the increasing emergence of prediagnostic psychopathologies that are captured in terms such as 'at-risk mental state' and 'attenuated psychosis syndrome' which can be [but are not necessarily] the harbingers of transition to a psychotic diagnosis (Insel, 2010; Brown, 2011; Carpenter, 2011; Waddington et al., 2012; Howes and Murray, 2014).

2. Dimensional perspectives of psychosis: psychopathology and mutant phenotypes

The extant literature focuses on at least five domains of psychopathology in psychotic illness [positive (psychotic) symptoms, negative symptoms, cognitive dysfunction, mania and depression], with psychosis being identifiable under 12 diagnostic categories [schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, bipolar disorder, major depressive disorder, substance-induced psychotic disorder, psychotic disorder due to a general medical condition, substance-induced mood disorder, mood disorder due to a general medical condition, psychotic disorder not otherwise specified] (van Os and Kapur, 2009; APA, 1994); yet broader dimensional schema have recently been advocated (APA, 2013). Thus, preclinical studies, and particularly those in genetically modified (mutant) mice, must go beyond seeking to model 'schizophrenia' and seek to reflect these diversities.

Where one is seeking to develop a valid animal model of an illness characterised by symptomatic and possible etiological heterogeneity, as well as diagnostic overlap with several other psychiatric disorders (e.g. ASD, ADHD, bipolar disorder, depression), a reductionist approach, where the syndrome is broken down into component parts, facilitates the development of more practicable animal models for those behavioural dimensions, rather than trying to recapitulate the entire disease phenotype (O'Tuathaigh et al., 2014). A well-rehearsed caveat, commonly stated during discussion of preclinical models of psychosis, is that the psychotic or 'positive' symptoms (e.g. hallucinations and delusions), as well as negative symptoms (e.g. poverty of speech and flattening of affect) may not be accessible in rodent models, thereby restricting model validation efforts to assessment of face and (in some cases) predictive validity (Low and Hardy, 2007; Young et al., 2009; Kirby et al., 2010; Papaleo et al., 2011; O'Tuathaigh et al., 2012; Moran et al., 2014). Behavioural models of positive symptoms have traditionally employed indirect dopamine (DA)-linked motor-based measures [e.g. novelty- and psychostimulant-induced hyperactivity], and/or pre-attentional and attentional phenomena such as prepulse inhibition (PPI) or latent inhibition (LI), paradigms; these reflect, respectively, sensorimotor gating and salience attribution processes known to be disturbed in schizophrenia (Moser et al., 2000; Braff et al., 2001; van den Buuse et al., 2009; Barak and