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Research report

Prepulse inhibition and genetic mouse models of schizophrenia

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ABSTRACT

Mutant mouse models related to schizophrenia have been based primarily on the pathophysiology of schizophrenia, the known effects of antipsychotic drugs, and candidate genes for schizophrenia. Sensorimotor gating deficits in schizophrenia patients, as indexed by measures of prepulse inhibition of startle (PPI), have been well characterized and suggested to meet the criteria as a useful endophenotype in human genetic studies. PPI refers to the ability of a non-startling "prepulse" to inhibit responding to the subsequent startling stimulus or "pulse." Because of the cross-species nature of PPI, it has been used primarily in pharmacological animal models to screen putative antipsychotic medications. As techniques in molecular genetics have progressed over the past 15 years, PPI has emerged as a phenotype used in assessing genetic mouse models of relevance to schizophrenia. In this review, we provide a selected overview of the use of PPI in mouse models of schizophrenia and discuss the contribution and usefulness of PPI as a phenotype in the context of genetic mouse models. To that end, we discuss mutant mice generated to address hypotheses regarding the pathophysiology of schizophrenia and candidate genes (i.e., hypothesis driven). We also briefly discuss the usefulness of PPI in phenotype-driven approaches in which a PPI phenotype could lead to "bottom up" approaches of identifying novel genes of relevance to PPI (i.e., hypothesis generating).

1. Introduction

Prepulse inhibition (PPI) of startle is a cross-species measure that refers to the ability of a non-startling "prestimulus" to inhibit the response to a startling stimulus ([96]; neurobiological reviews [64,190]). There have been numerous reports of PPI deficits in schizophrenia patients (for review see [19,197]), their unaffected first degree relatives [29], and patients with schizotypal personality disorder [28]. In addition to decreased PPI observed in schizophrenia patients, several other neuropsychiatric disorders are associated with decreased PPI, including Obsessive-Compulsive Disorder [189], Tourette's syndrome [192], Huntington's disease [195], manic bipolar patients [153], Panic Disorder [129], and adults with autism [154]. Thus, while there are several neuropsychiatric disorders that display decreased PPI compared to normal controls, PPI deficits in schizophrenia patients are the best characterized and the most widely replicated [19,114,128,130,197].

While the meaning of deficient or reduced PPI for an organism has been debated, Swerdlow et al. [197] have argued persuasively that it is a useful psychophysiological process for basic studies in humans and animals to probe neural circuitry and as a pharmacological screen. Additionally, PPI of startle has been suggested as a potentially useful endophenotype with which to understand the genetics of schizophrenia [18], meeting the criteria outlined for a viable endophenotype by Turetsky et al. [205]. Specifically, the endophenotype should be heritable, present in unaffected relatives, associated with a disorder with good test re-test reliability, able to be measured rapidly and easily, and have a discrete neurobiological basis that is related to the pathophysiology and genetics of a disease [205]. Hence, many in the field of schizophrenia genetics have focused primarily on neurophysiological measures such as PPI, P50 auditory evoked suppression, antisaccade eye movement, mismatch negativity, and P300 event related potential [205]. The assertion that PPI may be a useful endophenotype in genetic studies of schizophrenia, combined with the observation that PPI has a strong genetic component in mice [55], suggests that PPI may be a useful behavioral phenotype to consider in genetic mouse models related to schizophrenia. While there are certainly many other symptoms and deficits observed across the heterogeneous group of patients with schizophrenia, PPI appears to be a viable endophenotype for genetic studies and thus a reasonable approach to investigate in animal models of the genetics of schizophrenia. Mutant mouse models related to schizophrenia have been based primarily on the pathophysiology of schizophrenia, the known effects of antipsychotic drugs, and candidate genes for schizophrenia. In this review, we provide a selected overview of PPI in mouse models of schizophrenia and discuss the contribution and usefulness of PPI as a phenotype in the context of genetic mouse models. In a 2002 review of genetic mouse models of PPI, Geyer et al. [66] summarize studies of strain differences in PPI, genetic mutants, and

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the pharmacology of PPI in mice. More recently, there have been two particularly relevant reviews on mouse models of susceptibility genes for schizophrenia [143] and mouse models of altered PPI [197]. Hence, in order to avoid redundancy with these previous reviews, in the current review we highlight a few of the approaches to genetic mouse models of schizophrenia and discuss some of the important caveats to these approaches. To that end, we discuss mutant mice generated to address hypotheses regarding the pathophysiology of schizophrenia and candidate genes (i.e., hypothesis driven). We also discuss the usefulness of PPI in phenotype-driven approaches in which a PPI phenotype could lead to "bottom up" approaches of identifying novel genes of relevance to PPI (i.e., hypothesis generating).

1.1. How does prepulse inhibition relate to symptoms of schizophrenia?

Many reports in the literature argue that PPI in animals models the positive symptoms of schizophrenia. This conceptualization stems primarily from the observation that drug-induced deficits in PPI are produced by psychotomimetic drugs such as amphetamine and PCP, and that drug-induced PPI deficits are reversed by first generation antipsychotics, which are all dopamine D_2 receptor antagonists. In a recent review, Jones et al. [103] nicely outline the animal models that map onto the clinical symptoms of schizophrenia and accurately point out that there are no suitable animal analogs of hallucinations or delusions. Jones et al. [103] do suggest that two other "positive symptoms", psychomotor agitation and grossly disorganized behavior, may be assessed in animals through measures of locomotor response to novelty and patterns of motor activity, respectively. The misconception that PPI is a measure of the positive symptoms of schizophrenia most likely stems from the fact that models of PPI deficits (e.g., pharmacological disruptions) have been relatively successful in predicting antipsychotic medications, which are fairly effective at treating the positive symptoms of schizophrenia and less effective, if at all, at treating the negative symptoms and cognitive deficits in schizophrenia. Historically, of course, most drug development efforts have focused on the identification of antipsychotic treatments for the positive symptoms of schizophrenia, given that only these criteria were used to evaluate potential treatments for use in patients with schizophrenia.

Attempts to correlate PPI deficits with positive and negative symptoms have yielded mixed results [200]. Some studies have reported negative correlations between PPI and thought disorder [139,151,152] or distractibility [109] in schizophrenia. In a recent study comparing cognitive function with PPI in over 300 subjects, there were no correlations between PPI and cognition as measured by traditional "pen and paper" tests (i.e., Wisconsin Card Sorting Task [WCST], California Verbal Learning Task, etc.), however, there was a positive relationship between PPI and Global Assessment of Function (GAF) and Independent Living scales [193]. Nevertheless, studies assessing behavioral measures reflecting cognitive constructs have demonstrated relationships to PPI performance. For example, converging evidence indicates that PPI is correlated with strategy formation and execution time in the Cambridge Neuropsychological Test Automated Battery (CANTAB) in healthy controls [12,43,68], a finding which should be further examined in patients with schizophrenia. Further work is needed to specify the aspect of cognitive function that might be best related to gating processes such as PPI [215]. For example, the CNTRICS (Cognitive Neuroscience measures of Treatment Response of Impaired Cognition in Schizophrenia) program funded by the National Institute of Mental Health considered PPI to provide a measure of the cognitive construct of "gain control" as a specific aspect of the perceptual abnormalities seen in patients with schizophrenia [83]. The series of CNTRICS workshops concluded that PPI may have utility as a biomarker for use in proof of concept studies of potential treatments for the cognitive deficits in schizophrenia that are not ameliorated by existing antipsychotic drugs.

1.2. Utility of prepulse inhibition measures in genetic models of schizophrenia

For the purpose of evaluating a genetic mouse model of schizophrenia, the more useful comparison to make is not between PPI and specific symptoms of schizophrenia but rather the relationship between a gene and the observable dependent measure, i.e., PPI. As mentioned above, PPI has been suggested to meet the criteria as an endophenotype for genetic studies of schizophrenia [205]. The approach of using endophenotypes in schizophrenia in genetic studies has greatly strengthened the ability to conduct cross-species translational studies by providing specific observables or endophenotypes for study in experimental animals (reviewed in [65,80]). Useful endophenotypes in this context are measures that are observed in humans and can be measured in mice.

1.2.1. Hints to the role a gene may play in neural circuitry of PPI

Genetic manipulations have the potential to increase our understanding of the neural circuitry of neuropsychiatric disorders. A PPI deficit could indicate that the gene may be involved in the neural circuitry know to modulate PPI (e.g., cortical, limbic, striatal [190]); in other words it could function as a "surrogate measure for neural processes" as Swerdlow et al. [197] argue. For example, if a mouse is developed for a schizophrenia candidate gene with a relatively unknown function (or at least not an obvious relationship to schizophrenia pathology) and this mouse exhibits a PPI deficit, this may be an indication that limbic or striatal circuitry is altered. While a PPI deficit per se is not indicative of altered striatal or limbic circuitry, the presence of the deficit may suggest that these brain regions are affected by the genetic manipulation and provide a reasonable starting place for further hypothesis testing regarding the neurobiological implications of the genetic manipulation. Of course any evaluation of a PPI phenotype should be considered in the context of a thorough assessment of physical and sensory abnormalities (e.g., hearing loss), as pointed out in [66].

1.2.2. A pharmacological screen

Mutant mouse models offer the opportunity to screen putative antipsychotics that may involve a novel target. Most pharmacological studies of PPI are based primarily on the ability of a drug (e.g., dopamine D_2 antagonist) to reverse a drug-induced deficit in PPI (e.g., D_2 agonist; [64]). This approach can lead to what some have called "receptor tautology," meaning that a model based on the disruptive effects of a dopamine D_2 agonist may only be able to predict drugs that act as D_2 receptor antagonists. Using mutant mice to screen for putative antipsychotics may provide a means to develop novel drug targets. Several important examples of mutant mice being used to test putative antipsychotics are reviewed in subsequent sections.

1.2.3. A tool to study gene–environment interactions

Based on the diathesis-stress model of schizophrenia, which postulates that a genetic susceptibility coupled with environmental factors may be required for the full manifestation of the disease [79], studies of gene–environment interactions may be particularly informative for schizophrenia. Three ways in which genetics and environmental manipulations have been utilized in genetic mouse models are (1) using a mutant (e.g., knockout, KO) to delineate the mechanism of an environmental manipulation; (2) rescuing a phenotype in a mutant with an environmental manipulation; or (3) potentiating or unmasking a phenotype in a genetic mutant with an environmental manipulation (i.e., addressing the two-hit model