Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Sensorimotor gating deficits in "two-hit" models of schizophrenia risk factors

Asma Khan, Susan B. Powell *

Department of Psychiatry, University of California San Diego, 9500 Gilman Dr., La Jolla, CA 92093, United States
Research Service, VA San Diego Healthcare System, La Jolla, CA, United States

ARTICLE INFO

Article history:
Received 18 May 2017
Received in revised form 3 October 2017
Accepted 6 October 2017
Available online xxxx

Keywords:
Behavior
Development
Prepulse inhibition
Schizophrenia
Genetic
Risk factor
Double hit
Sensorimotor gating

ABSTRACT

Genetic and environmental models of neuropsychiatric disease have grown exponentially over the last 20 years. One measure that is often used to evaluate the translational relevance of these models to human neuropsychiatric disease is prepulse inhibition of startle (PPI), an operational measure of sensorimotor gating. Deficient PPI characterizes several neuropsychiatric disorders but has been most extensively studied in schizophrenia. It has become a useful tool in translational neuropharmacological and molecular genetics studies because it can be measured across species using almost the same experimental parameters. Although initial studies of PPI in rodents were pharmacological because of the robust predictive validity of PPI for antipsychotic efficacy, more recently, PPI has become standard common behavioral measures used in genetic and neurodevelopmental models of schizophrenia. Here we review "two hit" models of schizophrenia and discuss the utility of PPI as a tool in phenotyping these models of relevant risk factors. In the review, we consider approaches to rodent models of genetic and neurodevelopmental risk factors and selectively review "two hit" models of gene × environment and environment × environment interactions in which PPI has been measured.

1. Introduction: utility of prepulse inhibition in models relevant to schizophrenia

Sensorimotor gating occurs when a motor responses is gated by a sensory event. One form of sensorimotor gating that has been studied at multiple levels of biology, from its cellular mechanisms (Frost et al., 2003; Nusbaum and Contreras, 2004; Rose and Scott, 2003) to its relationship to neuropsychiatric disease (Braff, 2010, 2011; Swerdlow et al., 2008), is prepulse inhibition (PPI) of startle. PPI occurs when a weak, subthreshold stimulus presented 30–500 ms prior to an intense startling stimulus inhibits the startle response (Graham, 1975; Hoffman and Ison, 1980). The circuitry of PPI has been studied most extensively in rodents and involves role of cortico-striatal-pedunculopontine (CSPP) circuitry in which limbic and descending pontine projections modulate the ability of the prepulse to inhibit the startle response, which occurs at the level of the pons (Swerdlow et al., 2001a; Swerdlow et al., 2008). Thus, PPI provides an operational measure of sensorimotor gating and may indicate the integrity of the underlying neural circuitry subserving sensorimotor gating mechanisms. PPI is an integral part of human psychophysiological studies of neuropsychiatric disease and is amenable to neuroscience-based inquiry of deficits in functional domains. Indeed, in the Research Domain Criteria (RDoC) outlined by the National Institute of Mental Health, PPI is considered part of the "Auditory Perception" construct in the cognitive domain. In humans, startle to acoustic or tactile stimuli is most often measured from the eye blink response (Braff et al., 1992; Fridlund and Cacioppo, 1986; Kumari et al., 2003; Neuner et al., 2010; Swerdlow et al., 2001b). PPI deficits were first observed in schizophrenia patients (for review see Braff et al., 2001; Swerdlow et al., 2014; Swerdlow et al., 2008), but are also apparent in their unaffected first degree relatives (Cadenhead et al., 2000) as well as patients with schizotypal personality disorder (Cadenhead et al., 1993). A recent large, multi-site study reported PPI deficits in schizophrenia patients, corroborating the >40 single-site studies published to date (Swerdlow et al., 2014). PPI deficits, however, are not unique to schizophrenia and are also observed in several other neuropsychiatric disorders (Kohl et al., 2013), including Obsessive-Compulsive Disorder (Ahmari et al., 2012; Ahmari et al., 2016; Hoenig et al., 2005; Swerdlow et al., 1993), Tourette's syndrome (Buse et al., 2016; Castellanos et al., 1996; Swerdlow et al., 2001b), Huntington's disease (Swerdlow et al., 1995; Valls-Sole et al., 2004), manic bipolar patients (Perry et al., 2001), Panic Disorder (Ludewig et al., 2002), Fragile × syndrome (Frankland et al., 2004; Hessl et al., 2009), adults with autism (Perry et al., 2007), Asperger's Syndrome (McAlonan et al., 2002), 22q11 Syndrome (Sobin et al., 2005), nocturnal enuresis (Ornitz et al., 1992), and Kleinfelter Syndrome (van Rijn et al., 2011). Thus, PPI deficits are observed across many neuropsychiatric

* Corresponding author at: Department of Psychiatry, University of California San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0804, United States.
E-mail address: sbpowell@ucsd.edu (S.B. Powell).

https://doi.org/10.1016/j.schres.2017.10.009
0920-9964/

disorders but have been the most widely replicated in schizophrenia patients (Braff et al., 2001; Kumari et al., 2008; Ludewig et al., 2003; Mackeprang et al., 2002; Swerdlow et al., 2008).

PPI has been a useful behavioral phenotype to consider in genetic mouse models relevant to schizophrenia and other neuropsychiatric diseases (Powell et al., 2012). Additionally, because PPI measures basic information processing and can be quantified in multiple species, it is a useful tool for understanding the biology of putative risk genes. Indeed, over the last 20 years a large number of genetic mouse models have been tested for differences in PPI. These studies indicate that PPI can be either increased or decreased by a wide variety genes involved in neural development, neurotransmitter function, or basic cellular processes (Powell et al., 2009; Powell et al., 2012). Our recent review provided an update on mutant mouse models in which PPI was measured as a phenotype with comprehensive tables detailing PPI across a wide variety of mutant models and its pharmacological modulation, where appropriate (Powell et al., 2012). PPI has also proven to be a useful tool in evaluating the impact of environmental risk factors during development, which is covered briefly in Section 3.

Previous reviews summarized schizophrenia candidate genes (Arguello and Gogos, 2010; Arguello and Gogos, 2011; O'Tuathaigh and Waddington, 2015), while other reviews focused specifically on PPI, summarizing genetic mutants, strain differences, and the pharmacology of PPI in mice (Geyer et al., 2002; Powell et al., 2012; Powell et al., 2009; Swerdlow et al., 2008; van den Buuse, 2010), as well as recent reviews on models of gene × environment interactions (Ayhan et al., 2016; Moran et al., 2016). The etiology of schizophrenia is multifaceted and likely involves a convergence of both genetic and environmental risk factors (Cannon et al., 2003; Gottesman, 1991; Uher, 2014). Thus, experimental models evaluating gene-environment interactions are particularly informative for schizophrenia. In this review, we summarize approaches to rodent models of genetic and neurodevelopmental risk factors and selectively review "two hit" models of gene × environment and environment × environment interactions in which PPI has been measured. The review highlights approaches to combined risk factors for schizophrenia that have used PPI as a behavioral endpoint and discusses caveats of, and future directions for, double hit models.

2. Genetic landscape of schizophrenia

2.1. Approaches to genetic discoveries

The two primary approaches to understanding the genetics of neuropsychiatric disease are the common disease/common allele approach (CDCA) and the common disease/rare allele approach (CDRA) (Arguello and Gogos, 2011). Candidate gene or unbiased genome-wide association studies (GWAS) focus on common genetic variants (>5% allele frequency); whereas, the CDRA approach focuses on the hypothesis that rare variants with high penetrance can cause common disease (Arguello and Gogos, 2011). Schizophrenia and other major neuropsychiatric and neurodevelopmental conditions are likely a combination of risk from both common and rare variants.

The recent Psychiatric Genomics Consortium (PGC) genome-wide association study (GWAS) of schizophrenia (Consortium, 2014) identified 108 genetic loci associated with schizophrenia. Some of the most notable findings in the PGC are loci containing genes for G protein coupled receptor signaling, glutamate neurotransmission, neuronal calcium signaling, synaptic function and plasticity, other neuronal ion channels, and neurodevelopment (Consortium, 2014). Because these associations imply the existence of one or more risk variants at the locus rather than a specific gene, it is premature to discuss in depth the role of any specific genes at these loci until there is a more complete understanding of the risk variants and whether the variants are functional. As the basic biology of the identified loci begins to be investigated, there will certainly be many mouse mutants created to target those genes. One strategy for using the PGC GWAS data for neuroscience drug discovery put forth by Schubert and colleagues, is to prioritize gene targets based on knowledge of gene function and functional variants to identify putatively causal genes, and annotate these putatively causal genes with information on mRNA expression, de novo mutations, disease-associated rare mutations, and literature knowledge to determine targets for novel drug discovery (Schubert et al., 2014). A similar strategy could be taken by molecular biologists creating novel mouse mutants for basic biological interrogations of target genes. Another interesting finding emerging from large-scale GWAS studies across psychiatric disorders is the large degree of genetic overlap between schizophrenia and both autism spectrum disorder (ASD) and bipolar disorder, suggesting shared disease pathways or common risk. Thus, mouse models manipulating these genes should be considered a more general risk factor for multiple neurodevelopmental and/or neuropsychiatric disorders.

2.2. Genetics of PPI as an endophenotype

A complementary approach to large-scale GWAS or copy number variant (CNV) studies of schizophrenia are genetic studies of endophenotypes, which assume that the endophenotypemore proximal to the biological function of disrupted genes and/or be more easily and reliably quantified. Hence, psychophysiological processes such as PPI, have been used as endophenotypes in schizophrenia genetic studies (Braff et al., 2007; Greenwood et al., 2011; Greenwood et al., 2012; Greenwood et al., 2013) based on meeting criteria for a viable endophenotype (e.g. heritable, easily measured, good test-retest reliability; (Turetsky et al., 2007). PPI heritability has been estimated at 32%, which is similar to the 31% and 44% schizophrenia heritability estimates for nuclear and extended families, respectively, suggesting similar heritabilities for the disease and the endophenotype (Greenwood et al., 2007; Light et al., 2014).

Candidate gene studies indicated that polymorphisms in the CHRNA3 gene (Petrovsky et al., 2010), neuregulin 1 (Roussos et al., 2011), and COMT (Giakoumaki et al., 2008; Quednow et al., 2008; Roussos et al., 2008) are associated with PPI. In more recent studies of multiple SNPs using much larger sample sizes, however, only a few of these associations remained. In the larger, family-based COGS (Consortium on the Genetics of Schizophrenia) dataset, SNPs for CHRNA7, NCAM1, COMT, GRID2, CAMK2A were the most strongly associated with PPI, and NOS1AP, GRIK3, NRG1, GRIN3A, and DBH moderately associated with PPI (Greenwood et al., 2011). In a follow-up study based on non-familial samples from UCSD (Greenwood et al., 2012) only GRID2 achieved significance at more stringent significance levels. Other genes including GRIK3, CTNNA2, SLC6A3, SLC1A2, and GRIN2A were modestly associated with PPI. Across the endophenotypes studied in the UCSD and COGS samples, GRID2 and GRIK3 were significantly associated with PPI in both studies, strengthening the potential for these two genes to be promising genetic hits. The other gene that appeared across two separate studies was SLC6A3 (dopamine transporter gene). In addition to the modest association with PPI in the Greenwood et al. (2012) study, a genome-wide linkage analysis of the COGS sample suggested linkage (LOD score >2.2) for PPI on chromosome 5p15, a "gene dense" region that contains SLC6A3 (Greenwood et al., 2013), indicating that the dopamine transporter may be an additional gene of interest for follow up studies. Whether this endophenotype approach is more useful than genetic studies based on disease diagnosis is heavily debated in psychiatric genetics, but it is certainly complementary to GWAS studies of disease and may offer useful information regarding biological processes that cut across psychiatric diagnoses (Cuthbert and Insel, 2013).

2.3. Mutant mouse models: where to go from here?

McCarroll et al. (2014) argue that a new "biological playbook" needs to be written to address the new genetic discoveries emerging from unbiased genome-wide studies (McCarroll et al., 2014). The question for

Please cite this article as: Khan, A., Powell, S.B., Sensorimotor gating deficits in "two-hit" models of schizophrenia risk factors, Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.10.009