Online Discussions

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Forum Discussion: Cognition in Mouse Models of Schizophrenia Susceptibility Genes

In our Forum Discussion "journal club" series, the editors of journals provide access to the full text of a recent article. In this case, we thank the Schizophrenia Bulletin, not to mention Oxford University Press, for providing access to the full text of an article by Alexander Arguello and Joseph Gogos of Columbia University, New York City. A short introduction by Jim Koenig, of the Maryland Psychiatric Research Center, and author of SRF's Animal Models of Schizophrenia, gets us started, and then it's up to our readers to share their ideas and insights, questions, and reactions to the selected paper.


Background Text

By Jim Koenig, Professor, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore

Cognitive impairments remain as the most severely disabling symptom domain of patients afflicted by schizophrenia. The CNTRICS and MATRICS programs provided guidance for the identification of components of the cognitive domain that can be defined in patients with schizophrenia and that might be amenable to investigation in animal models for the disease. However, it is not clear whether these cognitive endophenotypes are related in terms of their pathophysiological bases. The use of well-defined genetic animal models and relevant cognitive endpoints may, however, begin to approach issues of common etiology, translatability, and potential pharmacological intervention strategies for components of the cognitive pathologies of schizophrenia.

The review authored by Arguello and Gogos describes the cognitive phenotypes present in genetic mouse models across the six domains of cognitive dysfunction articulated in the CNTRICS program. The authors focus their review on the mutant mouse preparations that are available for the top 30 candidate genes as identified 7 May 2009 in the SchizophreniaGene (SZGene) database. It is clear from this review that genetically manipulated mouse models are not available for all 30 of the leading candidate genes identified in the database. In addition, not all phenotypes have been tested in the available animal preparations. Nonetheless, this excellent review begins to analyze whether cognitive domains have a
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common genetic etiology or are only related at a behavioral level. Although the review is not exhaustive, there is sufficient detail provided to inform investigators about the state of this exciting area of research with strong clinical relevance. Some questions to consider include the following:

1. Are there one or two of these cognitive phenotypes that have more relevance or importance for improving the quality of life for a patient with schizophrenia?

2. There are many neurological diseases associated with cognitive dysfunction, including schizophrenia. Are there cognitive endpoints that may be more relevant to schizophrenia than other diseases?

3. Other than PPI and MMN, which of these cognitive endpoints, if any, could be exploited for high-throughput procedures?

4. The authors state: “The study of the mutant models reviewed above affords the opportunity to identify whether deficits within a cognitive domain converge merely at the behavioral level or whether there are common underlying neural correlates, and if so, how this may be related to diverse clinical phenotypes.” Does this approach really allow investigators to grasp the "neural correlates" that might be involved?

Comments on Online Discussion

Comment by: Craig M. Powell
Submitted 21 April 2010

The conclusion of this paper, that we need better behavioral tests of higher-order cognitive function in rodent models to better mimic cognitive dysfunction in schizophrenia, does not seem very controversial. Currently, it seems most important to create a model with high constructive validity, to understand how brain function is perturbed in each model, to understand in detail how behavior is altered in each model, and to try to reverse brain function abnormalities to "treat" the behavioral abnormalities. Any efforts to create high-throughput cognitive tasks in rodent models are welcome and should be incorporated into the search for behavioral abnormalities in these disease models.

View all comments by Craig M. Powell

Comment by: Jared Young
Submitted 6 May 2010

The review of Arguello and Gogos provides a timely reminder of the importance of assessing the cognitive performance of genetic models of schizophrenia. Moreover, they provide a very nice oversight on transgenic/mutant lines available to date to investigate cognition in schizophrenia and the work that has been done to phenotype these mice.

The majority of transgenic mice discussed, however, are not specific to mutations observed in schizophrenia patients. Although they do discuss DRD2 knockout mice, it is surprising they did not discuss α7 nAChR knockout mice, despite the obvious relation to attentional performance.

Another surprise was that despite the admission that animal tasks of working memory likely measure short-term, not working memory, a large part of the review discusses evidence of performance of transgenic animals in tasks that