Playing on Without AKT1: Subtle Cortical Deficits Suggest Vulnerabilities

21 November 2006. The enzyme AKT1 has been implicated in both schizophrenia and bipolar disorder. A new study in the November 7 issue of PNAS finds that a mouse lacking the gene for AKT1 shows subtle alterations of neuronal morphology in prefrontal cortex, as well as deficits in working memory. Joseph Gogos and Maria Karayiorgou of Columbia University in New York City also report that the absence of AKT1 primarily impacts molecular cascades involved in synaptic function, neuronal development, myelination, and actin polymerization in this cortical region.

Gogos and Karayiorgou first identified AKT1 as a candidate susceptibility gene for schizophrenia in 2004 (see SRF related news story), and it has been linked to bipolar disorder as well (Toyota et al., 2003). The association of the gene with schizophrenia has been supported in some, but not all genetic studies. Most recently, Bajestan and colleagues (2006) found a haplotype of the gene that increased risk for the disorder in an Iranian population.

Notably, AKT1 is a downstream target of dopamine D2 receptors, the main target of antipsychotic drugs. In their original paper, the Gogos and Karayiorgou groups focused on the possibility that altered AKT1 signaling via glycogen synthase kinase (GSK)3β might be involved in the either the pathophysiology of schizophrenia or in the action of antipsychotic drugs. Two subsequent studies have either supported (Zhao et al., 2006) or failed to support (Ide et al., 2006) the implication of altered AKT1/GSK3β signaling in schizophrenia. However, AKT1 is not a one-trick pony—it activates a number of other molecules.

How well does prefrontal cortex get along without AKT1?
In their current update on the AKT1-deficient mouse, first author Wen-Sung Lai and colleagues focus their attention on the prefrontal cortex (PFC), a region critical for working memory and believed by many to be especially vulnerable in schizophrenia. The researchers first report on their efforts to make sense of the myriad changes in gene transcription in prefrontal cortex resulting from AKT1 gene knockout in C57BL/6J mice. They sorted the up- or downregulated mRNA transcripts into functionally related groups, which converged on pathways involved in maintenance of the actin cytoskeleton, as well as more general categories such as neuronal development, synaptic transmission, and myelination. “In all, the combined pattern of concerted alterations in the expression of PFC-expressed genes unveiled by gene-class testing implies that AKT1-deficiency in vivo causes deficits in neuronal development and the establishment of local neuronal architecture and connectivity in PFC,” the authors write.

Lai and colleagues also report evidence of prefrontal cortical abnormalities on histological and behavioral analyses. Using a marker that preferentially labels layer V pyramidal neurons, the major output neurons of the neocortex, the researchers were able to quantify dendritic morphology in these cells. They report that in AKT1-null mice these neurons have a curious shift in morphology—the apical dendritic trees that extend up into more superficial layers are less complex, or “bushy,” than in wild-type mice, whereas the basal dendrites of lower cortical layers are more complex. There was no alteration in the density of dendritic spines in the AKT1 +/- mice.
**Probing working memory**

The researchers sought to reinforce their hypothesis of prefrontal cortical dysfunction in the AKT1 mice by testing for working memory deficits. After finding that the mutant mice exhibited normal working memory in T-maze experiments, Lai and colleagues tried to bring out more subtle deficits by perturbing different neurotransmitter systems. They found that a selective dopamine D2 receptor agonist caused AKT -/- mice to perform more poorly than wild-type mice in the working memory tasks, whereas activation of D1 receptors produced equivalent perturbations of working memory in both knockout and wild-type mice.

“The observation that the dopamine effect was specific for activation of [the] D2 class of receptors, in agreement with the observation that stimulation of D2 but not D1 class receptors results in a cAMP-independent dephosphorylation and inactivation of AKT, underscores the accuracy and validity of our analysis and indicates that AKT1 deficiency makes working memory performance more vulnerable to the effects of DRD2 but not DRD1 activation,” the authors write. They note that previous research has identified AKT1 as a downstream target of D2 activation and that antipsychotic drugs can affect AKT1 signaling.

Using agents that target other neurotransmitter systems, the researchers were also able to show that AKT1 -/- mice are more sensitive to perturbations in noradrenergic and cholinergic neurotransmission than wild-type mice.

Lai and colleagues acknowledge the huge challenge of tying perturbations in a knockout mouse model to the pathophysiology of schizophrenia, particularly if it is one gene among many susceptibility genes. “In all, the utility of the AKT1 mouse model (and any gene-based model) will critically depend on the experimental level of analysis, and can be enhanced in future experiments by combined modeling of more than one genetic risk factor, which can be achieved by crossing more than one engineered mouse strain or by combined modeling of genetic deficits and environmental influences,” the authors write.—Hakon Heimer.

**Reference:**


**Comments on News and Primary Papers**

**Comment by: Takeo Yoshikawa, Akihiko Takashima**

Submitted 30 November 2006

I recommend the Primary Papers

In this study, Karayiorgou and Gogos’s group have conducted a meticulous anatomical analysis of pyramidal cell dendritic structures in the prefrontal layer V cortex, as well as genome-wide expression and pharmaco-behavioral analyses, focusing on prefrontal functions in Akt1-deficient mice. The study examines the reduced (or altered) AKT1-GSK3β signalling theory of schizophrenia, proposed by this ([Emamian et al., 2004](http://www.schizophreniaforum.org/new/detailprint.asp?id=1301)) and other groups.

AKT1 as a genetic susceptibility gene for schizophrenia shows promise in the Caucasian population but this is not reflected in Asian populations as evidenced by our results ([Ide et al., 2006](http://www.schizophreniaforum.org/new/detailprint.asp?id=1301)). In addition, even in Caucasians, true causal variants have not been identified. Because of this, schizophrenia researchers are interested in observing disease-relevant
phenotypes in Akt1-deficient mice. In this study, they have detected morphological and functional alterations of frontal cortex-related traits in mutant mice using state-of-the-art techniques.

To further strengthen AKT1 as a candidate disease gene in schizophrenia, several issues need to be addressed in the near future. For instance, if a reduction of AKT1 signalling occurs in the brain, tau should be hyper-phosphorylated by activated GSK3β, which in turn will lead to the formation of neurofibrillary tangles (NFTs) as seen in Alzheimer’s disease. Therefore, it would be interesting to determine whether Akt1-deficient mice show a similar pattern of tau phosphorylation. Accumulating evidence suggests that hyper-phosphorylated tau may affect a variety of neuronal functions. Our recent biochemical analyses failed to reveal any significant reduction of AKT-mediated signalling in the prefrontal cortex of schizophrenic brains or the expected inverse correlation between phosphorylation levels of AKT and tau (Ide et al., 2006). This highlights the difficulty of examining protein phosphorylation status using postmortem brains, where results are often confounded by multiple, uncontrollable factors.

Another important but poorly understood point is the functional relationship among subspecies of the AKT family (at least AKT1, AKT2 and AKT3) and GSK3 (GSK3α and GSK3β) (for example see Sale et al., 2005). We look forward to continuing multidisciplinary studies aimed at unravelling the role of the AKT cascade, including the clarification of downstream pathways (Datta et al., 1999; (O’Mahony et al., 2006) in schizophrenia pathology.

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Related News: News Brief: Schizophrenia-linked AKT1 Variant Affects Brain Parameters

Comment by: Takeo Yoshikawa, Akihiko Takashima
Submitted 17 June 2008

Some researchers in the field of psychiatric genetics have become somewhat pessimistic about the ability to detect robust genotype-phenotype correlations using the diagnostic criteria defined by DSM-IV. If we analyze tens of thousands of samples, the ensuing results may be statistically robust, but still the effect of common variant(s) of each gene will be modest. Recently, Tan et al. (2008) reported that the AKT1 gene SNP rs1130233 and its encompassing haplotypes are significantly associated with IQ/processing speed, activities that may reflect frontal cortex function. They also showed that performance in their psychological test battery is influenced not only by AKT1 genetic variants but also the well-known COMT gene non-synonymous polymorphism (SNP rs4680, Val158Met). By undertaking fMRI analysis, they intertwined the IQ/processing speed-frontal cortex-AKT1 signal-DA system, i.e., the. integration of multidimensional disciplines. In citing references (Meyer-Lindenberg and Weinberger, 2006; Weinberger et al., 2001), they state that “there is a growing body of data showing that genes weakly associated with complex constellations of behavioral symptoms are much more strongly associated with in vivo brain measures.” Indeed, they have succeeded in explaining a possible role for AKT1 in brain execution capability, but have not provided convincing evidence for genetic associations between AKT1 and schizophrenia.
Their current results are elegantly derived from “a complex set of experiments addressing association of multiple variants in a gene with many phenotypic measures.” However, from a genetic perspective, we may still ask the following questions, irrelevant of the current study:

1. What is the genetic component (or heritability) of each psychological and imaging trait? Can variations in some of the psychological/cognitive/intellectual performances be fully captured by a single gene in an experimental set that examines, at the most, a hundred samples? We have learned the hard way from genetic association studies done in the 1990s, which examined a small number of samples, that we simply cannot trust those results. With regard to this point, the heritability calculations of so-called “endophenotypes” as reported by Greenwood et al. (2007) can give helpful information [also see Watanabe et al., 2007, supplementary Table S2]. There is the possibility that the genetic architecture of neurocognitive functions and imaging measures may not be simpler than the current disease category (entity).

2. Given the rapid advances in genotyping technology, we may be able to generate genome-wide genetic test results for every neuropsychiatric trait in the near future.

3. Because of the functional significance of AKT1 and the divergence in the signaling cascade downstream of AKT1, it would be wise to confine analysis to this gene. However, it is frustrating that we still do not know the functionally important SNP(s) of AKT1 in spite of numerous association studies.

4. Nackley et al. (2006) have convincingly demonstrated that the haplotype of the COMT gene constructed by synonymous SNPs has much more functional impact than the Val158Met polymorphism. Therefore, we would like to see the association studies examining this haplotype in future neuropsychiatric studies.

From a biochemical perspective, the following issues would be interesting and future targets for clarification:

1. The authors suggest that the coding synonymous variation of AKT1 affects protein expression, leading to the alteration of frontostriatal function and gray matter volume. The activity of AKT1 is regulated by its phosphorylation status. Therefore, readers would want to know whether the reduction of AKT1 expression levels actually affect the AKT signaling pathway. Behavioral analysis and an MRI study of Akt1 heterozygote knockout mice may provide relevant information.

2. Impairment of the AKT signal is known to result in tau hyperphosphorylation through activation of GSK3 as seen in Alzheimer disease brains. According to this idea, a reduction of AKT levels caused by SNP(s) should elicit hyperphosphorylation of tau and ultimately form neurofibrillary tangles (NFTs). In contrast, there are some reports suggesting the absence of NFTs and neuroinjury in elderly patients with schizophrenia (Arnold et al., 1998; Purohit et al., 1998). It is also reported that GSK3 is reduced in schizophrenia (Beasley et al., 2001). It would be interesting to know whether the genetic variation(s) of AKT1 that induce decreased protein expression affect tau accumulation.

3. Lithium inhibits the arrestin-Akt signal (Beaulieu et al., 2008). If so, it would be interesting to know whether lithium treatment can restore some of the effects of reduced AKT1 expression levels caused by the SNP(s) of interest.

References:

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