GSK3β—Not Just for Tauists Anymore

30 January 2004. Alzheimer's researchers sneak regular peeks over the shoulders of colleagues working on Parkinson's and other neurodegenerative diseases. Why not do the same with schizophrenia researchers, who are working in a disease that features hallucinations—an occasional feature of AD—and obvious deficits in working memory? Here, then, is such a peek: A paper in Nature Genetics, wherein researchers implicate impaired signaling in the AKT1-GSK3β pathway in schizophrenia.

The tauophiles in the Alzheimer's research community have a longstanding interest in glycogen synthase kinase (GSK)3β because it is known to phosphorylate tau (see ARF related news story), and those more drawn to the amyloid camp have also begun to show interest in the GSK3α variant, which could be involved in the production of Aβ (see ARF related news story). GSK3β is well-studied due to its role in regulating insulin and β-catenin in the Wnt pathway.

The major factor controlling GSK3β activation is the protein-serine/threonine kinase AKT1, which has already come to interest AD researchers for its role in inhibiting apoptosis. And the researchers have been quick to note that AKT1 mediates phosphatidylinositol 3 (PI3) kinase signaling, which in turn is susceptible to Aβ control. Psychiatric disease researchers have turned their attention to AKT1, which appears to be a principal target of lithium and other drugs used in bipolar disorder. There is some evidence that the AKT gene increases risk for bipolar disorder. Given the evidence for overlapping genetic and biochemical abnormalities in bipolar disorder and schizophrenia, AKT1 is also of great interest in schizophrenia research.

In the current study, a multi-institutional team led by Joseph Gogos of Columbia University and Maria Karayiorgou of the Rockefeller University, both in New York City, went on an interesting "fishing expedition." They write, "We speculated that alterations in brain levels or activity of protein kinases and phosphatases may contribute to schizophrenia susceptibility in humans and that this might be observed in the peripheral tissues of individuals with schizophrenia." Assessing protein levels in peripheral blood lymphocytes, they focused on kinases implicated in synaptic plasticity, and were rewarded with the finding that levels of AKT1 protein were 68 percent lower in subjects with schizophrenia (P = 0.014). This went hand-in-hand with significant decreases in phosphorylation of the AKT1 target GSK3β both in peripheral lymphocytes and in postmortem tissue from frontal cortex of schizophrenia patients. In addition, AKT1 levels were reduced in the cortex of patients.

The site of the AKT1 gene, in the cytogenetic band 14q32, has never been fingered as a susceptibility locus in linkage scans of kindreds with schizophrenia. However, the authors found a significant association between schizophrenia and a haplotype of the AKT1 gene associated with lower protein levels. In another experiment, the authors turned to AKT1 -/- mice to investigate whether these show any abnormalities that might be relevant to schizophrenia. They indeed found that this knockout strain produced deficits in a measure of sensorimotor gating, a defect characteristic of schizophrenia. In addition, the authors showed in-vivo evidence that haloperidol, much like lithium, boosts phosphorylation of AKT1, evidence that the AKT1-GSK3β pathway could be a prime site of action for the antipsychotic medication.

As catalogued by the authors, AKT1 turns up as a player in many cellular processes, with links to important molecules (e.g., GABRA, BDNF, NRATC, calcineurin, neuregulin), and thus is poised to have wide influence. "This influence may be additive, perhaps due to small impairment of several processes, or may be restricted to a small number of key processes that are particularly AKT1 dosage-dependent. In any case, our data is consistent with a model in which impairment of AKT1-GSK3β signaling increases the liability of these neuronal circuits to additional genetic or
environmental insults that ultimately lead to the disease," the authors conclude.—Hakon Heimer.

Reference: