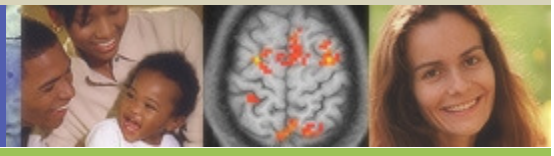

Science Update
January 23, 2008

Faster-Acting Medications for Bipolar Disorder's Manic Phase May Be Feasible

New Research Pinpoints Potential Molecular Target in Brain Cells

Scientists may be able to develop faster-acting medications for the manic phase of bipolar disorder, new research shows.

Current medications take several days to weeks to work, during which the extreme mood shifts of the disease may cause patients to engage in harmful behaviors, such as risky health behaviors or spending sprees. Bipolar disorder, also called manic-depressive illness, affects about 5.7 million Americans age 18 and older in any given year.

The faster medications would be aimed more directly at a molecular site on brain cells that current medications, such as lithium and valproate, reach through a slower, roundabout route. By targeting the site with a protein fragment they designed, NIMH scientists reduced manic-like behaviors and associated brain changes in rats. Jing Du, Ph.D., Husseini Manji, M.D., and colleagues published their results in the January 2 issue of The Journal of Neuroscience.

With further research, the molecular site could become a target for new medications for humans, or could point the way to other targets for new treatments, the scientists say. The site is an amino acid, serine 845 (S845), in the GluR1 subunit of the AMPA receptor. (See "About the Science.").

The researchers also pinpointed a region of the brain that appears to be involved in mania: the CA1 region of the hippocampus, which feeds stored memories to the prefrontal cortex, the "active-thinking" part of the brain.

About the Science

The molecular site scientists targeted with the protein fragment they designed is a protein building block – the amino acid S845 – of a receptor on brain cells. More precisely, S845 is a building block in one of several subunits that come together to form the receptor, called AMPA. Receptors are proteins, on or in cells, that affect cell function when brain chemicals bind to them.

AMPA receptors play a crucial role in brain cells. They receive chemical signals from other cells, helping trigger electrical impulses through which the cells communicate. The AMPA receptors are part of a larger system in the brain, the glutamatergic system, which is thought to become over-active in mania. Scientists have evidence that current medications work by dampening this system.

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Location, Location, Location

One of the subunits of the AMPA receptor, GluR1, plays a prominent role in this study. GluR1 subunits and other subunits have to be in the right place, at the right time, to join together to form AMPA receptors.

Under normal circumstances, the subunits that eventually will form the receptor can quickly change their locations in the cell, as needed, through chemical reactions. Current medications for mania also cause therapeutic changes in the locations of the subunits and the receptor. For example, they reduce excess levels of the GluR1 subunit on the cell surface.

But current medications take time to affect this process. Scientists suspect that this is because the molecular targets the medications initially act on must have trickle-down effects that eventually reach crucial targets – perhaps days or weeks later.

In a series of experiments, NIMH scientists showed that the S845 building block of the GluR1 subunit may be a crucial target. Targeting S845 alone brought about several positive changes in the locations of GluR1 and another important subunit of the AMPA system, GluR2, in rat-brain cells, and corrected behaviors in rats made manic with amphetamines.

Why S845?

The scientists took aim at S845 in the GluR1 subunit because they suspected that the roundabout route current medications take to relieve mania symptoms eventually leads there.

This site serves as an "on switch" for the GluR1 subunit. When a phosphate molecule binds with S845, the subunit goes into action, helping to form more AMPA receptors and to drive them to the surface of the cell, where their presence fosters electrical excitability among cells – which, in excess, is thought to contribute to mania. The protein fragment the researchers designed prevented phosphate molecules from binding with S845 in the GluR1 subunit.

Reference: Du J, Creson TK, Wu L-J, Ren M, Gray NA, Falke C, Wei Y, Wang Y, Blumenthal R, Machado-Vieira R, Yuan P, Chen G, Zhuo M, Manji HK. The Role of Hippocampal GluR1 and GluR2 Receptors in Manic-like Behavior. The Journal of Neuroscience, 2008 28: 68-79; doi:10.1523/JNEUROSCI.3080-07.2008. January 2008.