Gene regulatory protein is reduced in bipolar disorder

October 25 2011

Low levels of a brain protein that regulates gene expression may play a role in the origin of bipolar disorder, a complex and sometimes disabling psychiatric disease. As reported in the latest issue of *Bipolar Disorders*, the journal of The International Society for Bipolar Disorders, levels of SP4 (specificity protein 4) were lower in two specific regions of the brain in postmortem samples from patients with bipolar disorder. The study suggests that normalization of SP4 levels could be a relevant pharmacological strategy for the treatment of mood disorders.

"We found that levels of SP4 protein in the brain's prefrontal cortex and the cerebellum were lower in postmortem samples from patients with bipolar disorder, compared with samples from control subjects who did not have the disease," said co-senior author Grace Gill, PhD, an associate professor in the department of anatomy and cellular biology at Tufts University School of Medicine and a member of the neuroscience; genetics; and cell, molecular and developmental biology program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts.

Gill's laboratory team at Tufts collaborated with researchers from Spain and used postmortem samples from Spain's University of the Basque Country brain collection program to examine SP4 protein levels in samples from 10 bipolar subjects and 10 control subjects matched for gender, age, and time since death.

The team focused on the prefrontal cortex and the cerebellum because

brain imaging studies suggest that bipolar disorder is associated with changes in the structure of these brain regions. Little is known about the cellular and molecular changes that occur in bipolar disorder, especially in the cerebellum.

"Our findings suggest that reduced activity of the SP4 protein may be common in bipolar disorder," stated co-senior author Belén Ramos, PhD, a former postdoctoral fellow in Gill's lab and now a researcher at the Parc Sanitari Sant Joan de Déu (PSSJD) and the Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) in Barcelona, Spain.

Ramos explained that SP4 belongs to a category of proteins known as transcription factors, which regulate gene expression. "While this study examined the SP4 protein levels, mutations in the gene encoding the SP4 protein have been associated with psychiatric diseases including bipolar disorder, a poorly understood disease characterized by episodes of abnormally elevated energy levels with or without depressive episodes, as well as schizophrenia, and major depressive disorder. Thus, our study adds to the growing body of evidence that alterations in gene regulation contribute to the development of psychiatric disorders," said Ramos.

Further analysis showed that SP4 levels are regulated by neuronal activity, indicating that this transcription factor is important for normal neuronal signaling. "Looking at normal rat neurons in culture, we found that SP4 is rapidly degraded by enzymes in the absence of neuronal signaling, which we refer to as the non-depolarized state," said first author Raquel Pinacho, BS, MS, a graduate student in Ramos' lab in PSSJD.

In previous work, the researchers had identified an essential role for SP4 in regulating the structure of nerve cells during development. Taken together, the findings suggest that reduced levels of this protein may

contribute to altered patterns of nerve cells in the brain.

"Moreover," added Ramos, "we demonstrated that the destruction of SP4 by enzymes was inhibited by lithium, a drug widely used as a mood stabilizer for patients with bipolar disorder. When lithium was added to cells in the non-depolarized -- inactive -- state, levels of SP4 were stabilized and increased. This finding suggests that the therapeutic effects of lithium may be related, at least in part, to changes in gene expression leading to changes in cellular structure and function."

In addition to measuring levels of SP4, Gill and colleagues assessed levels of SP1, a related transcription factor protein that has been reported to be altered in schizophrenia. Like SP4, SP1 was reduced in the cerebellum of subjects with bipolar disorder. According to the authors, this finding suggests that both factors may be relevant transcriptional regulators, low levels of which may contribute to the pathogenesis of bipolar disorder and other psychiatric diseases. However, unlike SP4, levels of SP1 did not appear to be regulated by neuronal activity, highlighting the complexity of the mechanisms involved in functional specificity in the SP transcription factor family.

More information: Pinacho R, Villalmanzo N, Lalonde J, Haro JM, Meana JJ, Gill G, Ramos B. Bipolar Disorders. "The transcription factor SP4 is reduced in postmortem cerebellum of bipolar disorder subjects: control by depolarization and lithium." Published online October 21, 2011, doi: 10.1111/j.1399-5618.2011.00941.x

Provided by Tufts University

disorder.html