Molecular mechanism links stress with predisposition for depression

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A new study provides insight into how stress impacts the brain and may help to explain why some individuals are predisposed to depression when they experience chronic stress. The research, published by Cell Press in the January 27 issue of the journal *Neuron,* reveals complex molecular mechanisms associated with chronic stress and may help to guide new treatment strategies for depression.

"Many individuals exposed to stressful events do not show signs or symptoms of depression; however, some individuals exposed to psychological stress are predisposed to major depression," explains senior study author, Dr. Yoshifumi Watanabe, from Yamaguchi University in Japan. "Thus far, the molecular mechanisms underlying the susceptibility and adaptation to chronic stress within the brain are poorly understood."

Dr. Watanabe, coauthor Dr. Shusaku Uchida and their colleagues used two genetically distinct mouse strains that exhibit different behavioral responses to chronic stress to look for genetic mechanisms associated with vulnerability to stressful events. The researchers observed that, in contrast to the stress-resilient mice, the stress-vulnerable mice exhibited depression-like behaviors when exposed to chronic mild stress (environmental and social stressors that do not include food or water deprivation).

The stress-vulnerable mice had a lower level of gene expression for glial cell-derived neurotrophic factor (Gdnf). Neurotrophic factors are known to be important for regulation of brain plasticity and have been implicated in depression. The reduced level of Gdnf expression was the result of DNA methylation and histone modifications. These changes, called epigenetic modifications, and the depressive behaviors were reversed by treatment of the stress-vulnerable mice with antidepressants.

"Dynamic epigenetic regulations of the Gdnf gene play important roles in determining both the susceptibility and the adaptation responses to chronic stressful events," concludes Dr. Uchida. "Elucidation of the mechanisms underlying the modulations of HDAC2 expression, histone modifications, and DNA methylation influenced by chronic mild stress could lead to novel approaches for the treatment of depression."

Provided by Cell Press