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Lack of protein FKBP51 in old mice improves resilience to depressive behavior

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Decreasing expression of a protein associated with susceptibility to depression made old mice resistant to depressive-like behavior while improving their hormonal response to stress, a study led by researchers at the University of South Florida found. The lack of this protein, FKBP51, did not adversely affect their memory, learning, or basic motor functions.

The study suggests that drug discovery efforts aimed at reducing levels of the protein FKBP51 may yield new antidepressant therapies. The findings appear online today (Sept. 15, 2011) in the journal PLoS ONE.

The multidisciplinary research team included scientists from Vanderbilt University Medical Center and the University of Texas at El Paso as well as the USF Health Byrd Alzheimer's Institute.

"About a third of patients are resistant to treatment with standard antidepressant medications, so we need to look for other potential therapeutic targets," said principal investigator Chad Dickey, PhD, assistant professor of molecular medicine at the USF Health Byrd Alzheimer's Institute.

"We've shown that, because FKBP51 appears to act on the genetic liability to abnormal mood and anxiety states, it may offer a much needed treatment tool for secondary prevention of depression recurrence and relapse."

Dickey and his colleagues were using a mouse model with the FKBP5 gene deleted to help study the potential role of the protein it produces, FKBP51, in the progression of Alzheimer's disease. The protein increases with old age, and a reduction of FKBP51 levels has been shown to decrease the burden of tau, a hallmark protein associated with Alzheimer's disease.

FKBP51, a protein encoded by the FKBP5 gene, is highly expressed in the hypothalamus-pituitary-adrenal (HPA) axis, a major part of the brain's circuitry that controls neuroendocrine system responses to stress. Human genetic studies over the last decade have indicated that slight variations in the FKBP5 gene are associated with increased susceptibility to psychiatric disorders, including depression, post-traumatic stress disorder and anxiety.

The researchers decided to examine for the first time whether old mice without the FKBP5 gene (and its protein by-product) were more resistant to depression using behavioral tests that routinely evaluate antidepressant effectiveness. They exposed two groups of old mice (17 to 20 months) to activities designed to induce depressive/stressed behavior. One group was FKBP5 deficient, while the other (littermates) was not.

"We wondered if the FKBP5-deficient mice would demonstrate more resilience, or greater antidepressant behavior, in response to the tests," said lead author John O'Leary, a PhD student in neuroscience at the USF Health Byrd Alzheimer's Institute.

They did, and without any apparent adverse consequences. The FKBP5-deficient mice performed as well as their littermates with the FKBP5 gene intact on tasks designed to test memory, learning and basic motor functions.

In an experiment coinciding with the observed effects on depression, the

researchers discovered that corticosterone levels rose as expected in both the FKBP5-deficient mice and their non-deficient counterparts following a stressful activity. However, the amount of corticosterone circulating in the blood of the FKBP5-deficient mice was still lower than that measured in the non-FKBP5 mice. Corticosterone (known as cortisol in humans) is a steroid hormone released in response to stress and its levels are higher than normal in depressed patients.

The researchers suggest that the lack of the protein FKBP51 leads to a decrease in HPA-axis activities, including a weakening of stress hormones, which may improve resilience to depression.

More information: A new anti-depressant strategy for the elderly: Ablation of FKBP5/FKBP51; John C. O'Leary III, Sheetal Dharia, Laura J. Blair, Sarah Brady, Amelia G. Johnson, Melinda Peters, Joyce Cheung-Flynn, Marc B. Cox, Gabriel de Erausquin, Edwin J. Weeber, Umesh K. Jinwal and Chad Dickey; PLoS ONE; published Sept. 15, 2011. dx.plos.org/10.1371/journal.pone.0024840

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