

## Gene-Regulating Protein Identified That Battles Inescapable Stress

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Researchers have identified a gene-regulating protein in the brains of mice that triggers the animals' ability to cope with the "behavioral despair" caused by inescapable stress. They said their studies have yielded an animal model of resilience that they will use to explore how antidepressants work on the brain circuitry involved in such stress response.

Led by Eric Nestler, the researchers published their findings in the journal *Neuron*, published by Cell Press.

In earlier studies, Nestler and his colleagues showed that exposure to repeated stress caused an increase in a protein called  $\Delta$ FosB in the brain. This protein is a "transcription factor," a regulatory protein that controls the activity of multiple target genes.

In the new experiments, they sought to explore the role of  $\Delta$ FosB in regulating adaptation to stress. Their approach involved first exposing mice to random shocks from which the animals could not escape. Such repeated exposure to inescapable stress tends to increase the lag time for mice to escape subsequent shocks, when they are given the chance to escape. Measuring this lag time, or the complete failure to escape, gave the researchers a measure of "behavioral despair." This experimental approach has long been used as an animal model of human "affective disorders" such as depression, posttraumatic stress disorder, and bipolar disorder. As in humans with such disorders, this behavioral despair in mice responds to antidepressants.

Nestler and colleagues discovered that the mice that showed the smallest lag in escape times also had higher levels of  $\Delta$ FosB in a brain region involved in processing of pain signals and defensive responses. In contrast, animals with either longer escape lag times or failure to escape showed lower  $\Delta$ FosB levels.

What's more, when the researchers introduced higher levels of the gene for  $\Delta$ FosB into mice, they found it reduced the level of behavioral despair as reflected in their readiness to escape shocks.

The researchers also established that increased  $\Delta$ FosB levels in the mice decreased the activity of the gene for a protein called "substance P<sub>1</sub>" known to regulate processes such as mood, pain sensitivity, anxiety, and stress

"Our present results provide a fundamentally novel and testable model for the mechanisms of resilience," concluded the researchers. "Our future studies will test the hypothesis that antidepressant treatments may enhance resilience by stimulating these same adaptive processes which occur spontaneously in some, but not all, of the individuals in a population exposed to chronic stress," they wrote.

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The researchers include Olivier Berton, Herbert E. Covington 3rd, Nadia M. Tsankova, Tiffany L. Carle, Paula Ulery, Akshay Bhonsle, Vaishnav Krishnan, Shari Birnbaum, and Eric J. Nestler of The University of Texas Southwestern Medical Center, Dallas; Michel Barrot of European Neuroscience Institute of Strasbourg and Unit Mixte de Recherche 7519, Centre National de la Recherche Scientifique/Universit Louis Pasteur, Strasbourg; Karl Ebner, Georg M. Singewald, and Nicolas Singewald of University of Innsbruck, Innsbruck; Rachael L. Neve of Harvard Medical School, McLean Hospital, Belmont.

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Berton et al.: "Induction of  $\Delta$ FosB in the Periaqueductal Gray by Stress Promotes Active Coping Responses." Publishing in *Neuron* 55, 289-300, July 19, 2007. DOI 10.1016/j.neuron.2007.06.033.  
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