A brain chemical that battles despair

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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 July 19, 2007, issue of 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 ΔFosB 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 ΔFosB 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 ΔFosB 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 ΔFosB levels.

What's more, when the researchers introduced higher levels of the gene for ΔFosB 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 ΔFosB levels in the mice decreased the activity of the gene for a protein called "substance P¡" 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.

Source: Cell Press