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Protein found linking stress and depression

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(PhysOrg.com) -- Stress, the ever-present threat to health and happy living, is tough on the brain. If the strain goes on too long, it can lead to debilitating psychological problems. Part of the reason, according to scientists at The Rockefeller University, may have to do with a little-known family of proteins called kainate receptors that has recently been implicated in major depression. New research in rats may help explain one mechanism by which stress reshapes the brain: namely, by ramping up production of a particular part of these proteins.

We've recently seen large human studies that suggest kainate receptors are targets for response to certain antidepressants and are also involved in major depression and the susceptibility to suicidal thoughts," says Richard Hunter, a postdoctoral fellow in Bruce S. McEwen's Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at Rockefeller. "We are trying to build up a molecular understanding of what is going on here."

In experiments published recently in a special issue of *PLoS ONE*, Hunter and his colleagues homed in on one of five subunits of the kainate receptor called KA1. Performing a series of experiments exploring the impact of stress and steroids on rats, they found that stress, simulated by restraining the rats for six hours a day for three weeks, caused the genes to send instructions — messenger RNA — to increase production of KA1 subunits in particular parts of the hippocampus, a highly plastic brain structure involved in learning and memory.

The lab produced a similar result by injecting unstressed rats with

hormones called corticosteroids, suggesting that an increase in these hormones is largely responsible for the stress response in rats. But the researchers also found that the dose is critical. While a moderate amount of corticosteroids increased KA1 messenger RNA, a high dose of the steroids did not. The relationship between the hormone and its impact is an inverted U response, a pattern familiar to biologists.

“The body seeks to maintain ideal levels, whether it is salts in the blood or any number of other things like KA1,” Hunter says. “Deviations to either side of these levels can cause pathologies or changes. The body adapts to changing circumstances to keep the levels healthy.”

Stress and depression are known to cause a reversible retraction of dendrites in certain brain cells, particularly in the hippocampus, that McEwen and colleagues refer to as “adaptive plasticity.” The new research suggests that an increase in KA1, caused by the corticosteroid response in rats, may trigger this retraction. The finding follows recent work by Rockefeller’s Sidney Strickland, head of the Laboratory of Neurobiology and Genetics, that showed that KA1 production explodes in the hippocampus during simulated stroke in mice, driving a cell-death cascade that begins when part of the brain is deprived of blood. Combined, the work suggests that the relatively understudied KA1 subunit plays an important role in a key area of the brain in both causing damage in an uncontrolled trauma such as a stroke and in protecting the brain from damage under the more controlled circumstances of chronic stress.

McEwen and colleagues have shown that healthy brains are remarkably resilient in the face of stress — brains replace their retracted neurons once the stress is removed. Perhaps, the researchers say, the same will prove true for depression. “One of the great hopes is that these changes in the hippocampus that happen with prolonged depression may not be signs of permanent irreversible damage but they may actually be signs of

plasticity that we can treat with appropriate medications and also behavioral therapies," McEwen says.

More information: Public Library of Science ONE 4(1): e4328 (January 30, 2009), Regulation of Kainate Receptor Subunit mRNA by Stress and Corticosteroids in the Rat Hippocampus, Richard G. Hunter, Rudy Bellani, Erik Bloss, Ana Costa, Katharine McCarthy and Bruce S. McEwen

Provided by Rockefeller University