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Acute stress leaves epigenetic marks on the hippocampus

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(PhysOrg.com) -- Scientists are learning that the dynamic regulation of genes -- as much as the genes themselves -- shapes the fate of organisms. Now the discovery of a new epigenetic mechanism regulating genes in the brain under stress is helping change the way scientists think about psychiatric disorders and could open new avenues to treatment.

In trying to explain psychiatric disorders, genes simply cannot tell the whole story. The real answers are in the interaction of genes and the environment. Post-traumatic stress disorder requires some trauma, for instance, and people, for the most part, aren't born depressed. Now research has revealed one mechanism by which a stressful experience changes the way that genes are expressed in the rat brain. The discovery of "epigenetic" regulation of genes in the brain is helping change the way scientists think about psychiatric disorders and could open new avenues to treatment.

Richard Hunter, a postdoc in Rockefeller University's Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, found that a single 30-minute episode of acute stress causes a rapid chemical change in DNA packaging proteins called histones in the rat hippocampus, which is a brain region known to be especially susceptible to the effects of stress in both rodents and humans. The chemical change Hunter examined, called methylation, can either increase or decrease the expression of genes that are packaged by the histones, depending on the location of the methylation. He looked for methylation on three regions of histone H3 that have been shown to actively regulate gene expression.

In experiments published this month in Proceedings of the National Academy of Sciences, he shows that methylation of one mark, H3K9 trimethyl, roughly doubled in the hippocampus. Methylation of a second mark, H3K27 trimethyl, dropped by about 50 percent in the same area. Changes associated with the third mark were minor.

“The hippocampus is involved in episodic memory, so you would expect it to be sensitive to episodic experiments like this, more so than the motor regions, for instance,” says Hunter, who worked on the project with Rockefeller scientists Bruce S. McEwen and Donald W. Pfaff. “But what is surprising is the magnitude and regional specificity of these patterns.” The sheer size of the change in histone methylation suggests that it is important to the brain’s response to acute stress, although its exact role remains a mystery. The two methyl marks that changed are both thought to repress gene expression usually, but methylation increased in one and decreased in the other.

Hunter also checked for similar changes as a result of chronic stress — exposure to a 30-minute stress each day for 21 days. He did not find a major effect, which could reflect the animals’ adjusting to the stress. However, when he treated the rats with fluoxetine, the generic form of the popular antidepressant Prozac, he reversed some methylation effects associated with chronic stress.

It’s becoming increasingly evident, Hunter says, that the epigenetic changes like the methyl marks he observed and others, such as acetylation and phosphorylation, could play a significant role in the brain’s response to stress and the treatment of stress related diseases, such as post-traumatic stress disorder.

“There was a thought that the genome project would reveal all in neuropsychiatric disease, but that has proven not to be the case,” he says. “Epigenetics has become much more interesting because it allows us to

look at how gene expression is changed by environmental events, explainable in part by histone modifications."

Provided by Rockefeller University (news : web)