UT SOUTHWESTERN MEDICAL CENTER NEWS

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EMBARGOED UNTIL 11 A.M. CDT THURSDAY, OCT. 18, 2007

Ability to handle stress, depression linked to variations in brain structure and function

DALLAS – Oct. 18, 2007 – Researchers at UT Southwestern Medical Center have found in mice that the ability or inability to cope with stress is linked to specific differences in the way brain cells communicate with each other.

Understanding these mechanisms – which are also present in people – may aid scientists in developing methods for humans to boost resilience to stress and depression.

"One of the major insights provided by this work is that resilience to stress is an active process," said Dr. Eric Nestler, chairman of psychiatry and senior author of the study, which appears in the Oct. 19 issue of *Cell*.

"This means that chronic stress, depression, post-traumatic stress disorder and similar disorders might be treated by promoting the mechanisms that underlie resilience," said Dr. Nestler.

Mice, like humans, vary widely in their reactions to stress. Some adapt well, while others become timid and appear depressed. While stress is known to play a major role in human mental illness, scientists wonder why some people can cope well with adversity while others do not.

The researchers used male mice that had been inbred to the point that they were genetically identical. They stressed the rodents by placing them in the territory of a larger, aggressive mouse and recorded how this stress affected their ability to interact socially. In a previous study, Dr. Nestler and his colleagues established that mice which repeatedly go through this "social defeat" are a good model for human depression.

In the current study, some of the genetically identical mice interacted with the unfamiliar, more aggressive mouse, while others avoided it and showed submissive behavior.

The researchers classified the mice according to whether they had coped with the stress or not. They found that some showed a long-lasting social withdrawal, while others continued to interact normally with other mice.

The mice that coped less effectively were also less attracted to sugar but more to cocaine than the coping mice, suggesting that there was a link between their vulnerability to stress and substance abuse.

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The researchers then examined two areas of the brain that are associated with pleasure and reward, called the ventral tegmental area (VTA) and the nucleus accumbens (NAc).

Neurons in the VTA send chemical signals to the NAc, and the present study shows that in mice experiencing social defeat and depression, these neurons fire faster. Upon firing, the neurons cause the release of a substance called BDNF, a nerve growth factor that the researchers have previously linked to poor coping.

The researchers further found that the vulnerable mice showed an increase in BDNF in the nucleus accumbens. The resilient ones did not, presumably because neurons from their VTAs did not fire as much. When the researchers genetically blocked BDNF in the more timid mice, they became resistant to stress.

"Preventing BDNF signaling to the nucleus accumbens may be a key mechanism of resistance to stress and depression," Dr. Nestler said.

The researchers also found that better-coping mice had far more genes turned on and off in the VTA and NAc than vulnerable mice. This discovery suggests that successful coping with stress is an active process that involves the regulation of many genes, not just the lack of responses seen in poorly coping animals.

Three of the genes that showed the greatest difference between the two groups of mice coded for potassium channels, molecules that let potassium pass through a nerve cell's membrane when it fires. The researchers found that the resilient animals had increased activity of the potassium channels, which counters the increased nerve firing, and hence the increase of BDNF release, in the vulnerable mice.

To explore how these results might apply to humans, the researchers obtained brain samples from depressed and non-depressed humans. The depressed people showed a 40 percent increase in BDNF levels in the nucleus accumbens, compared to controls.

From these various findings, the researchers concluded that preventing BDNF release into the nucleus accumbens may be a way to increase coping ability to stress or depression.

"It may be possible to develop compounds that improve one's ability to cope with stress," Dr. Nestler said. "But blocking BDNF might also affect other systems, so we must find a way to focus on this single pathway."

Vaishnav Krishnan, an M.D./Ph.D. student in the Medical Scientist Training Program and lead author of the paper, said, "The study yields significant insights into molecular mechanisms that may

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underlie individual differences of people in reacting to stressful life events."

Other UT Southwestern researchers involved in the study were Quincey LaPlant, William Renthal and Paul Tannous, all Medical Scientist Training Program students; Robin Reister and Ami Graham, research assistants in psychiatry; Drs. Danielle Graham, Diane Lagace and Thomas Green, all postdoctoral researchers in psychiatry; Drs. Scott Russo and Sumana Chakravarty, assistant instructors of psychiatry; Drs. Ming-Hu Han, Olivier Berton, Michael Lutter and Arvind Kumar, instructors of psychiatry; Drs. Subroto Ghose, Amelia Eisch and Donald Cooper, assistant professors of psychiatry; Drs. David Self and Howard Gershenfeld, associate professors of psychiatry; and Dr. Carol Tamminga, vice chairman of psychiatry.

Researchers from Harvard University and Cornell University also participated in the study.

The work was supported by the National Institute of Mental Health and the National Alliance for Research in Schizophrenia and Depression.

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