UT SOUTHWESTERN MEDICAL CENTER NEWS

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Social stress in mice is controlled by genetic pathway, researchers find

DALLAS – Feb. 9, 2006 – Deleting a specific gene in the brain has the same effect that antidepressants do in mice that have been conditioned to be depressed, report researchers at UT Southwestern Medical Center.

Mice are normally social animals, easily approaching and greeting unfamiliar mice. But when the strange mice are aggressive, a mouse over time becomes timid and withdrawn. Administering antidepressants such as Prozac improves their behavior, but so does deleting a gene called *BDNF*.

UT Southwestern researchers say conditioning mice to be withdrawn provides a new model for researching not only depression, but also other human ailments such as social phobia and post-traumatic stress disorder. In addition, deleting the *BDNF* gene can help track a biochemical pathway of depression in the brain, the researchers report in the Feb. 10 issue of the journal *Science*.

"This study provides new evidence of the importance of reward pathways in the brain in an animal's responses to social stress, and by extension to depression. It also provides some insight into the underlying molecular events involved," said Dr. Eric J. Nestler, chairman of psychiatry the study's senior author.

Dr. Nestler and his colleagues exposed mice to daily bouts of "social defeat," in which they encountered aggressive mice that overcame them in fights. This training went on for 10 days. The mice eventually became "defeated," no longer approaching unfamiliar mice. Even four weeks later, the defeated mice avoided other mice, not only their former bullies but even smaller and more docile mice.

When given the antidepressant drugs Prozac or Tofranil, the defeated mice's social interaction improved. The importance of the antidepressant use was that it worked over a long period, not just short-term, thus resembling human treatment, Dr. Nestler said.

"It's been hard for researchers to find a condition in animals that responds to chronic administration of antidepressants," he said. "This is one of the few tests in which animals respond to chronic antidepressants, rather than acute antidepressants, and that's a very important part of this study because antidepressants only work in humans after long-term administration."

The researchers also focused on a protein called BDNF, which helps regulate the release of the neurotransmitter dopamine, a key substance that carries signals from one nerve cell to another, in the brain's reward pathway.

In examining the role of BDNF (a type of nerve growth factor) in the mice's behavior, the

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researchers concentrated on two connected areas of the brain involved in pleasure and addiction: the ventral tegmental area, a dopamine-rich center in the primitive part of the brain, and the nucleus accumbens, a small area in the front part of the brain that receives strong dopamine signals from the ventral tegmental area.

Normal mice have BDNF in the ventral tegmental area, but a minimal amount in the nucleus accumbens. The defeated mice showed an increased amount of BDNF in the nucleus accumbens.

Researchers hypothesized that the ventral tegmental area may be the source of BDNF in the nucleus accumbens and that this BDNF is important in shaping behavior. To test this possibility, the researchers used viral gene transfer to delete the BDNF gene in the ventral tegmental area. Mice lacking the gene did not become depressed when exposed to bullies, showing that BDNF signals from the ventral tegmental area to the nucleus accumbens are critical for animals to learn aspects of social experiences.

The loss of withdrawn behavior in mice lacking the *BDNF* gene echoes the behavior of mice treated with antidepressants, the researchers said. Moreover, removal of the *BDNF* gene induced many of the same long-lasting changes in the nucleus accumbens as caused by chronic antidepressant treatment. The researchers concluded that BDNF is essential in shaping changes in nerve pathways and behavior associated with social stress.

The next step is to record the electrical activity of brain cells in the reward pathway in the mice as they undergo these tasks, said Dr. Olivier Berton, instructor of psychiatry and the study's lead author.

"We're trying to understand this response to stress from the molecular to the cellular to the neural circuit level of understanding," he said.

Other UT Southwestern researchers involved in the study were Drs. Colleen McClung and Lisa Monteggia, assistant professors of psychiatry; Dr. David Self, associate professor of psychiatry; Vaishnav Krishnan, William Renthal and Nadia Tsankova, students in the Medical Scientist Training Program; and Drs. Scott Russo and Danielle Graham, postdoctoral research fellows of psychiatry. Drs. Ralph Dileone, assistant professor now at Yale University School of Medicine; Carlos Bolanos, postdoctoral research fellow now at Florida State University; and Maribel Rios of Tufts University School of Medicine also participated.

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