

SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS FIND CLUE TO UNDERSTANDING TOLERANCE TO DRUGS OF ABUSE

DALLAS – Sept. 23, 2002 – Researchers at UT Southwestern Medical Center at Dallas and their colleagues have uncovered new information that will help brain researchers better understand a person's tolerance to drugs of abuse and open new avenues of investigation into the relationship of addictive-drug usage and the biological causes of mood disorders.

Dr. Michel Barrot, assistant professor of psychiatry at UT Southwestern and lead author of the paper, said researchers used genetically altered mice to show that pain – both physiological and psychological – as well as pleasure can activate changes in the nucleus accumbens, the forebrain structure critical for reward and motivation processes. The findings appeared in a recent issue of *Proceedings of the National Academy of Sciences*.

Senior author Dr. Eric Nestler, chairman of psychiatry at UT Southwestern, had previously established that drugs of abuse activate CREB, a specific binding protein known for playing a role in the plasticity and adaptation of nerves in the nucleus accumbens. This action between a drug and a binding site is involved with the learning processes and can affect the interaction between subject and environment.

Barrot worked with Nestler on the earlier research that laid the scientific basis for the study in *Proceedings*.

Researchers reported that they used viral-mediated gene transfer to deliver and overexpress CREB locally, thus mimicking the CREB hyperactivity seen after the delivery of drugs of abuse or exposure to stress. The mice were then tested for their sensitivity to rewards, such as morphine or sucrose, as well as for their sensitivity to anxiety-causing negative situations or painful stimuli.

“In the paper we show that inducing local CREB hyperactivity decreases the emotional response of an animal in different ways, including those that are rewarding, aversive, anxiety-provoking or hurtful,” Barrot said. “On the other hand, a decrease in activity in the CREB site

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causes the opposite reaction. These data suggest the CREB activity in the shell of the nucleus accumbens controls the behavioral responses to emotional stimuli.”

Barrot said the manipulation of the behavioral responses to the emotional stimuli “appears to be independent of either positive or negative intensity of the stimulus.”

Nestler said, “This work supports the view that brain-reward regions important for addiction may also be involved in symptoms of depression and implicates the critical role of CREB in controlling the activity of these brain regions.”

Researchers from Yale University, Harvard Medical School, the University of Washington in Seattle and Cold Spring Harbor Laboratory contributed to the paper, published in the Aug. 20 issue of *Proceedings*. Other UT Southwestern researchers are Dr. Linda Perrotti, research fellow; Dr. Ralph J. DiLeone, assistant professor; Dr. Olivier Berton, research fellow; Dr. Amelia Eisch, assistant professor; and Dr. Venetia Zachariou, visiting professor, all in the Department of Psychiatry.

The research was supported by the Human Frontier Science Program, the National Institute on Drug Abuse, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and the National Alliance for Research on Schizophrenia and Depression.

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