SOUTHWESTERN NEWS

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# RESEARCHERS AT UT SOUTHWESTERN, ROCKEFELLER ATTACK RIDDLE OF COCAINE ADDICTION AT MOLECULAR LEVEL

DALLAS – March 15, 2001 – Researchers at UT Southwestern Medical Center at Dallas and Rockefeller University have uncovered new information about dopamine-related activity in the brain that may lead to better understanding of the long-term brain-cell changes associated with cocaine addiction and addiction recovery.

Their findings are published in today's issue of *Nature*.

The research targets specific changes related to two brain proteins following the administration of cocaine, which may go a long way in explaining the chemical process that changes brain pathways and cellular activity following multiple exposure to cocaine, said Dr. Eric Nestler, one of the authors of the paper, "Cdk5 regulates action of chronic cocaine."

Nestler is chairman of psychiatry at UT Southwestern. A renowned researcher in the molecular brain activity of drugs and alcohol and their effects on the brain, Nestler came to UT Southwestern in 2000 after serving as director of molecular psychiatry at Yale University and as a member of the Yale faculty since 1987.

"This study provides important information about how the brain reacts to cocaine after repeated administration," Nestler said. "Little is understood about the brain mechanisms involved in the demands for more and more of the stimulant. We do know that the user has to increase the dose to achieve the expected high. This study gives us insight into the way the drug works in the brain to produce chemical changes that lead to addiction. If we understand how the process works, we will then be able to develop methods of countering the interaction."

Nestler and his colleagues found that injecting cocaine into the brains of transgenic mice over a period of time led to changes in a brain-specific protein cyclin-dependent kinase 5, or Cdk5, which is triggered by changes in the levels of another protein, ΔFosB. In earlier studies

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these same researchers had established that Cdk5 leads to brain-cell changes thought to play a major role in cocaine addiction by regulating dopamine action. Dopamine, a chemical communicator involved in the passing of pleasurable sensations to the limbic area of the brain, is associated with the reputed "rush" of cocaine.

Nestler said that injecting cocaine repeatedly into mice causes accelerated motor activity, even doubling it in some cases. Increases in Cdk5 appear to counter this stimulated activity since it can be augmented when the animals are treated daily with a Cdk5 blocker, or inhibitor, called roscovitine.

The group of control animals that received daily doses of roscovitine doubled their motor activity in just an hour after being injected with cocaine, leading to the hypothesis that once the pathways are changed by continual exposure to cocaine, more of the drug is required to reach a "high."

"We believe that this study provides important information about how the brain adapts to increased levels of cocaine, giving us important insight not only to the mechanism of cocaine use but to that of other drugs," Nestler said.

Nestler worked with Dr. James Bibb, Dr. Paul Greengard and their colleagues at Rockefeller on the study, which was funded by the National Institute on Drug Abuse. Researchers from Yale; Kurume University School of Medicine in Fukuoka, Japan; and Florida State University also worked on the study.

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