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Media Contact: Donna Steph Hansard
214-648-3404
donna.hansard@utsouthwestern.edu

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Gene controlling circadian rhythms linked to drug addiction, UT Southwestern researchers find

DALLAS – June 13, 2005 – The gene that regulates the body's main biological clocks also may play a pivotal role in drug addiction, researchers at UT Southwestern Medical Center have found.

The *Clock* gene not only controls the body's circadian rhythms, including sleep and wakefulness, body temperature, hormone levels, blood pressure and heart activity, it may also be a key regulator of the brain's reward system.

UT Southwestern researchers showed that, in mice, the *Clock* gene regulates the reward response to cocaine, suggesting that similar actions take place in humans. Findings from the multi-center study are available online in the *Proceedings of the National Academy of Sciences*.

"We found that the *Clock* gene is not only involved in regulating sleep/wake cycles, but is also very involved in regulating the rewarding responses to drugs of abuse," said Dr. Colleen A. McClung, assistant instructor of psychiatry at UT Southwestern and the study's lead author. "It does so through its actions on dopamine pathways."

Dopamine is a neurotransmitter associated with the "pleasure system" of the brain, providing feelings of enjoyment from certain activities. Dopamine is released by naturally rewarding experiences such as food, sex and the use of certain drugs.

In the study, mice that lacked the *Clock* gene were injected with cocaine. Not only did the mice experience problems with their circadian cycles – not sleeping as much and becoming more hyperactive – they also found cocaine more rewarding than control mice, demonstrated by their strong preference for the location where the drug was administered.

In addition, *Clock*-deficient mice produced more dopamine than control mice did, suggesting that the gene controlling circadian rhythms is a key regulator of the brain's reward system and may influence the addictive properties of drugs such as cocaine.

"We tracked dopamine cells in the mice brains and found that these cells fired more rapidly and showed a pattern called bursting, which leads to an usually large dopamine release," Dr. McClung said.

"We also found that more dopamine is produced and released in these mice under normal conditions and particularly after exposure to cocaine."

Dr. Eric Nestler, chairman of psychiatry at UT Southwestern and the study's senior author, said the results suggest there may be a link in disruption of circadian rhythms and the tendency to abuse drugs.

"Most work on *Clock* has focused on the brain's master pacemaker, located in a brain area called the suprachiasmatic nucleus," said Dr. Nestler. "The novelty of Dr. McClung's findings is the role *Clock* plays in brain reward pathways. The next step is to examine *Clock* and related genes in human addicts."

Dr. Donald Cooper, assistant professor of psychiatry at UT Southwestern, also contributed to the study, as did researchers from the University of Crete in Heraklion; the Rosalind Franklin University of Medicine and Science in North Chicago; and the Howard Hughes Medical Institute at Northwestern University.

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