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Addiction Keeps Its Own Clock

The *Clock* gene, widely appreciated as a driver of circadian rhythms, has now been shown to aid in regulating the brain's reward circuitry, which is triggered by drugs of addiction, such as cocaine. The findings from this study and others continue to build the case that *Clock* is a key cog in the machinery that drives an ever widening range of behaviors.

The researchers, including Howard Hughes Medical Institute investigator Joseph S. Takahashi at Northwestern University, published their findings June 13, 2005, in the early online edition of the *Proceedings of the National Academy of Sciences*. Other co-authors include Eric J. Nestler and colleagues from the University of Texas Southwestern Medical Center, the University of Crete and the Rosalind Franklin University of Medicine and Science in Chicago.

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Studies by Takahashi and other researchers have revealed that *Clock* regulates other genes involved in the biological clock machinery. Most biological clocks operate on a 24-hour, circadian (Latin for "about a day") cycle that governs functions such as sleeping and waking, rest and activity, fluid balance, body temperature, cardiac output, oxygen consumption and endocrine gland secretion.

However, said Takahashi, there had also been intriguing connections between circadian rhythms and the effects of drugs of addiction. For example, drug addiction is associated with disruptions in sleep and circadian rhythmicity. And animal studies have shown a circadian effect of drug self-administration, which suggested that there may be a connection between the brain's circadian and reward pathways.

More direct evidence of such a link has come from experiments with fruit flies by Jay Hirsh and colleagues at the University of Virginia, who found that mutant flies lacking some genes in the circadian pathway showed altered

behavioral responses to cocaine.

In the latest experiments, Takahashi and his colleagues studied the effects of cocaine administration on mice that carry a mutant *Clock* gene. In one experiment, they placed the *Clock*-defective mice in a test chamber, in order to study how cocaine affected their activity. However, he said, even the act of placing the mutant animals in the new environment yielded interesting results.

“When the *Clock* mutants were put into the test chamber, the first surprising thing was that even before the cocaine was given, they were more active in the novel environment than wild-type controls,” said Takahashi. “We hadn’t seen this before, because we just measured *Clock* mutant mice in their home cages. So, we were seeing a heightened response to novelty, we believe.” After the researchers began to administer cocaine, they found that the mutant mice responded with greater activity than did normal mice.

The researchers next gauged the level of reward the mice experienced in response to cocaine by first teaching them to associate receiving cocaine with being in one of two connected chambers. The subsequent preference of the mice for a particular chamber was a measure of the reward they received from the cocaine. These experiments revealed that the mutant mice had a heightened reward response to cocaine, when compared to normal mice.

The researchers also used *Clock* mutant mice to measure effects of the *Clock* gene had on the brain's reward circuitry, which is activated by the neurotransmitter dopamine. They found higher electrophysiological activity of dopamine-triggered neurons in a major reward area of the animals' brains. They also found that the mutant mice showed higher levels of an enzyme that is key to dopamine production in the area of the brain that processes reward response. More broadly, they found that the mutant mice showed decreased activity of a number of circadian genes known to be activated by *Clock*.

“These findings suggest a very different and unexpected role of these circadian genes from the traditional way we have thought about their effects,” said Takahashi. “Before, we would have assumed that the circadian clock was modulating such a process as the response to drugs, perhaps due to the influence of the time of day. But in this case, it looks as if the *Clock* gene itself is an upstream regulator of the mechanism involving dopamine in a very interesting part of the brain, where the reward pathway is located.”

According to Takahashi, the latest findings add to previous studies in his laboratory, in which it was found that *Clock*-defective mutant mice show a metabolic disorder. The mice show weight gain, elevated blood glucose and insulin insensitivity, he said.

“Our future studies will seek to understand whether behavioral and metabolic alterations are a result of the effects of the *Clock* gene itself, or of the genes it regulates,” said Takahashi.