SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS DISCOVER GENE IMPACTS OPERATION OF BODY'S INTERNAL CLOCK

DALLAS – July 3, 2003 – Removing a gene that helps control the body's internal clock dramatically changes patterns of sleep, activity and feeding in mice, researchers at UT Southwestern Medical Center at Dallas have discovered.

Their findings could explain why some species – including humans – function more efficiently at certain times of the day. The study is published online today in *Science* Express and will appear in a future print edition of the journal.

"Circadian rhythms have been studied for a long time, and most of the focus has been on the suprachiasmatic nucleus (SCN), a specialized region of the brain. It is the master pacemaker that controls all our rhythms – wakefulness and sleep, feeding and hunger," said Dr. Steven McKnight, chairman of biochemistry and senior author of the study.

In mammals, the SCN responds to changes in the light/dark cycle. It is turned on during the day and off at night by the transcription factor CLOCK (Circadian Locomotor Output Cycles Kaput). Neuronal PAS domain protein 2 (NPAS2), which Dr. McKnight discovered previously, is similar in structure to CLOCK but is found in forebrain areas that respond to inputs such as sound, smell and touch. The UT Southwestern researchers looked at the importance of these stimuli in controlling circadian behaviors by studying activity, sleep patterns and adaptability to changes in meal time in mice lacking NPAS2. They found that NPAS2 and CLOCK serve distinct roles in regulating circadian rhythms.

"The NPAS2 protein facilitates the ability of mice to adapt to circadian changes in their environment," said Carol Dudley, senior research scientist in biochemistry at UT Southwestern and lead author of the study. "Most of the time when you think about circadian rhythms, you think of fluctuations linked to light/dark cycles. That is important, but there are many other cues in our environment that tell us whether it's day or night. NPAS2 allows the body to respond to timing cues other than dark or light."

As nocturnal animals, mice are awake, active and feeding mostly at night. The researchers found that *Npas2*-deficient mice have no trouble keeping a normal circadian cycle

(MORE)

as long as food was available during the night. But when challenged with a paradigm where food was available only for a short period during a normally inactive time of day, the NPAS2-deficient mice could not adapt.

"When you try to shift their feeding behavior from night to day, wild-type mice adapt within a few days by consuming a huge amount of food during the day," Ms. Dudley said. "But mice that lack *Npas2* have a very hard time adjusting. They refuse to eat when it is light. They get the same input about food availability as the wild-type mice, but they don't translate that information into the correct behavior."

It took the *Npas2*-deficient mice up to 10 days to adjust to the changes in feeding cycles, the researchers found. But when these same mice were challenged with a shift in the light/dark cycle, *Npas2*-deficient mice were superior in synchronizing their activity to the new cycle.

"This implies that when the *Npas2* gene is absent, the animals become virtual slaves to light. When the *Npas2* gene is present, the mice are able to synchronize incoming somatosensory cues with the light/dark cycle to produce a robust circadian cycle," she said.

Dr. McKnight said the discovery has many implications for future research.

"We know that if you restrict food to the daytime period, wild-type mice will eat during the day and adapt their behavior," he said. "What we found in this study is that the forebrain adapts. Instead of turning genes on at nighttime, it turns them on during the day. Stimulatory impact forces the internal clock to shift. It's the same thing we see in shift workers, who can adapt to a new schedule at odds with our normal daytime activity within three or four days."

Other UT Southwestern researchers involved in the study are Claudia Erbel-Sieler, researcher in biochemistry; Sandi Jo Estill, research assistant in biochemistry; and Dr. Martin Reick, postdoctoral research in biochemistry. Researchers from Stanford University and Columbia University also participated in the study.

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