Disruption of circadian rhythm could lead to diabetes

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Disruption of two genes that control circadian rhythms can lead to diabetes, a researcher at UT Southwestern Medical Center has found in an animal study.

Mice with defective copies of the genes, called CLOCK and BMAL1, develop abnormalities in pancreatic cells that eventually render the cells unable to release sufficient amounts of insulin.

"These results indicate that disruption of the daily clock may contribute to diabetes by impairing the pancreas' ability to deliver insulin," said Dr. Joseph Takahashi, an investigator with the Howard Hughes Medical Institute at UT Southwestern and co-senior author of the study, which appeared in the journal *Nature*. Dr. Takahashi, who recently joined UT Southwestern as chairman of neuroscience, performed the research with colleagues when he was at Northwestern University.

Circadian rhythms are cyclical patterns in biological activities, such as sleeping, eating, body temperature and hormone production.

The mammalian CLOCK gene, which Dr. Takahashi discovered in 1997, operates in many tissues of the body to regulate circadian rhythms. The gene codes for a protein called a transcription factor, which binds to other genes and controls whether they become active. BMAL1 also codes for a transcription factor that works together with the CLOCK protein.

The researchers examined pancreatic islet beta cells, which secrete insulin when blood sugar levels increase. They genetically engineered some mice to have defective CLOCK genes and some to also lack the BMAL1 gene. The mice also were engineered to contain a bioluminescent molecule that allowed the researchers to detect the circadian clock in pancreatic cells as a fluctuating glow.

Normal islet cells glowed in a 24-hour rhythm, while cells with defective CLOCK genes showed nearly flat rhythms. Cells from different organs exhibited different circadian rhythm patterns, indicating that each organ controls its own internal clocks.

Further study showed that the islet cells in the mutant animals created normal amounts of insulin, but the CLOCK mutant cells were defective in releasing the hormone.

Mice with defective CLOCK genes were prone to obesity and other signs of metabolic syndrome and liver dysfunction. Young mice lacking the BMAL1 gene only in their pancreas, however, had normal body weight and composition, and their behavior followed normal circadian patterns, although their blood sugar levels were abnormally high, the researchers found.

"This finding indicates that disruption of clock genes only in the pancreas, and not the rest of the body clock, can produce early signs of diabetes," Dr. Takahashi said "These studies are important because they show a direct link between the clock in pancreatic beta-cells and glucose regulation. This should aid our understanding of the causes of glucose abnormalities."

Provided by UT Southwestern Medical Center