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Genes controlling insulin can alter timing of biological clock

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The biological clock was know to regulate metabolism. Now new evidence shows that metabolic processes can also alter the timing of the clock. Credit: Patera Design/UCSD Bio Sci

Many of the genes that regulate insulin also alter the timing of the circadian clock, a new study has found.

Although insulin responses were known to follow daily rhythms, the finding that components of the insulin-control system can reset the body's clock surprised the study's authors and suggests new approaches to treating disorders such as metabolic syndrome that can result, at least in part, from chronic disruption of the sleep-wake cycle.

"People knew that the clock regulates many different processes, but what they didn't realize what that when you tweak those processes, it feeds back and alters the clock," said Steve Kay, Dean of the Division of Biological Sciences at the University of California, San Diego, who led the study along with John Hogenesch of the University of Pennsylvania.

Several other important physiological control systems shift the clock as well, they report online this week in the journal *Cell*.

A molecular clock controls daily physiological rhythms in many types of cells, even cells grown in culture. By engineering cultured cells to glow yellow when a particular clock gene switched on, the team made the cycle visible. They then interfered with every human gene to see which would shift the clock. Hundreds altered the timing.

"We just suddenly discovered 350 new genes that affect the clock that weren't known before," Kay said. Subsequent screening to confirm the genes' effect on a second clock gene narrowed the list to 200.

Genes belonging to four systems appeared on the "hit" list more often than chance would predict: insulin and folate metabolism, and two systems that govern the life cycle and fate of cells. Seven genes involved in insulin control also influenced the rhythms of the clock.

"What came out very strongly was this close relationship between circadian regulation and insulin signaling," Kay said. "There's a reciprocal relationship between circadian dysfunction and metabolic dysfunction."

Genetically altered mice with malfunctioning clocks become obese and develop diet-induced diabetes, Kay points out. And studies of humans forced into a kind of chronic jetlag have seen marks of the onset of metabolic syndrome.

"Understanding this close relationship between circadian regulation and metabolic homeostasis should provide novel ways of identifying new therapies for metabolic disease," Kay said.

The wealth of data the team has created will also serve as a resource for other scientists who study circadian rhythms, Kay said. They have deposited data describing how each gene alters the rhythm of the clock to an open-access genetics database called BioGPS, along with a new "plug-in" application that displays the cyclical response.

Scientists working with Kay at UC San Diego are currently following up on some of the links between the clock and insulin control. Kay also serves on the scientific advisory board of ReSet Therapeutics, a venture that aims to discover and develop potential dugs to treat illnesses that result from chronic disruption of circadian rhythms.

Additional co-authors include Eric Zhang, Andrew Liu, Tsuyoshi Hirota, Loren Miraglia, Genevieve Welch, Xianzhong Liu, Jon Huss, Jeff Janes and Andrew Su of the Genomics Institute of the Novartis Research Foundation; and Pagkapol Pongsawakul and Ann Atwood of UC San Diego.

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