Molecular partnership controls daily rhythms, body metabolism

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A research team led by Mitchell Lazar, MD, PhD, Director of the Institute for Diabetes, Obesity, and Metabolism at the University of Pennsylvania School of Medicine, has discovered a key molecular partnership that coordinates body rhythms and metabolism.

Lazar and his colleagues, including the study's first author Penn Veterinary Medicine doctoral student Theresa Alenghat, studied a protein called NCoR that modulates the body's responses to metabolic hormones. They engineered a mutation into mice that prevents NCoR from working with an enzyme that is normally its partner, HDAC3. These animals showed changes in the expression of clock and metabolic genes, and were leaner, more sensitive to insulin, and on different sleep-wake cycles than controls.

The role of the NCoR-HDAC3 partnership in regulating the body's internal clock was previously unknown. HDAC3 is an enzyme that affects gene expression by binding to receptors in the cell nucleus to affect gene activity, but not by directly changing DNA. The findings suggest that HDAC via NCoR controls the body's internal clock, and therefore metabolism, through this epigenetic change. Their findings are reported in this week's issue of *Nature*.

"In the fight against the obesity and diabetes epidemics, disruption of NCoR and its enzyme partner, might be a valuable new weapon," says Lazar.

Most physiological processes cycle every day and night, and the most well-known of these circadian rhythms is the sleep-wake cycle. Abnormal sleep patterns, such as those of shift-workers, can be risk factors for metabolic disorders such as obesity and diabetes. "These diseases have reached epidemic proportions, so scientists are urgently seeking to understand the connections between biological rhythms and metabolism," notes Lazar.

The daily rhythm of mice with the disrupted molecular partnership was shortened by almost half an hour. Over time, this added up to a shifted daily rhythm.

The mice were also leaner (not gaining as much weight when put on a high-fat diet), and they were protected from developing resistance to the action of insulin, which is a hallmark of the most common form of diabetes in people. Expression of several metabolic genes was also altered in the engineered mice.

"The molecular partnership regulates hormone action as well as clock genes that coordinate circadian rhythms," says Lazar. "It's extraordinary that, despite their abnormal sleep-wake cycle, which might have been predicted to cause metabolic problems, the mice were actually healthier metabolically.

"However this finding doesn't mean people should start changing their sleep patterns because this is really evidence that there is coordination between metabolism and circadian activities, including sleep," cautions Lazar. "It's not that the mice are sleeping less, it's that their sleep cycle is shifted, when compared to mice maintained on a normal sleep-wake cycle."

Source: University of Pennsylvania