A 'dented' internal clock provides insight into shift workers' weight gain and diabetes

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A study of "dented" internal clocks seems to have provided evidence for a theory as to why people who work late or irregular hours are susceptible to weight gain and diabetes. High rates of shift workers gain weight and develop diabetes, which has been attributed to a mismatch between their internal clocks and their schedules, so researchers from the Perelman School of Medicine at the University of Pennsylvania created a related mismatch by altering the function of a molecule within the brains of mice that shortened their circadian rhythms from 24 to 21 hours. These mice gained more weight, had higher blood sugar, and fattier livers, all of which were corrected by changing their environment to a 21-hour "day."

"When the external world doesn't match the internal body's cycles, metabolism pays the price," said the study's senior author, Mitchell A. Lazar, MD, Ph.D., the director of Penn Medicine's Institute for Diabetes, Obesity, and Metabolism, and the Ware Professor of Diabetes and Metabolic Diseases. "We saw this in our study, and we believe that this happens similarly when people work odd hours that don't align with how human bodies are wired."

Published today in *Science Advances*, the researchers led by Lazar and primary investigator Marine Adlanmerini, Ph.D., a post-doctoral researcher in Lazar's lab, sought to explore circadian desynchrony, a theory in which a disruption or alteration to a person's innate, internal clock leads to poor outcomes. Shift workers—those who may work long hours, overnight, or with irregular rest periods in between work—are subject to this, which could be why they appear to be at higher risk for obesity, diabetes, and metabolic diseases including having a liver that retains more fat.

So to explore whether circadian desynchrony is a viable explanation for this, the researchers removed certain molecules called REV-ERB, which reside in the brain cells of mice, and seem to control the body's internal clock, holding it around 24-hour cycles. When REV-ERB was deleted, it caused the mouse body clocks to run roughly three hours shorter, which the researchers determined by tracking their regular sleep/awake pattern.

While their body clocks ran faster, some of these mice were kept in a typical day's 24-hour cycle, with 12 hours of light and 12 of dark. Those mice, when on their regular diet, were able to keep their weight in check. But when given a diet with higher contents of fat and sugar—a diet not unfamiliar to the typical American—they gained more weight and had more adverse conditions, like diabetes and fatty liver. Moreover, the mice who still had REV-ERB but were given the high-fat and sugar diet did not have the same high amounts of poor outcomes.

"One potential explanation is that the internal clock of the mice missing REV-ERB was running at odds with the 24-hour day, which led to metabolic stress on the body," Lazar said.

A way that was "fixed" was when the researchers adjusted the length of the mice's "day" in the lab to match their malfunctioning internal clock: 21-hour days with 10.5-hour cycles of light and dark to match their 21-hour internal clock. When this happened, the mice with the altered clocks no longer were as susceptible to the ill-effects of the unhealthy diet.

That correction seemed to fall in line with the circadian desynchrony theory: Once the internal clock and the day lined up again, metabolism appeared to operate at its normal, healthy rate.

"This may be a lesson for how to prevent or reduce obesity and diabetes in shift workers," Lazar explained. "For example, timing of meals to

better match the shift worker's own clock could be of benefit. That would also be consistent with a number of studies in mice and people that have suggested that eating at specific times of day may improve weight control and metabolism."

Moving forward, Lazar, Adlanmerini, and their team feel that potentially finding biomarkers which could be tested for and indicate how a person's internal clock is running would be key.

"Information like that could then be matched to decisions about when to eat, much as blood sugar monitoring can help a diabetic understand when they should be taking more insulin," said Lazar.

More information: Marine Adlanmerini et al, REV-ERB nuclear receptors in the suprachiasmatic nucleus control circadian period and restrict diet-induced obesity, *Science Advances* (2021). DOI: 10.1126/sciadv.abh2007

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