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Gut Microbiome May Be Key Link Between Jet Lag and Obesity

Beth Skwarecki | October 16, 2014

Gut microbes may be a key link between jet lag and obesity, according to research done in mice and confirmed in two humans. Mice whose daily rhythms were disrupted showed changes in the populations of bacteria in their gut and gained weight more easily on a high-fat diet than did mice whose rhythms remained stable.

The data, presented in an article published online October 16 in *Cell*, could provide a mechanism for common metabolic changes seen in humans with disrupted circadian rhythms, including frequent flyers and shift works, according to Christoph A. Thaiss, from the Department of Immunology, Weizmann Institute of Science, Rehovot, Israel, and colleagues.

The investigators first took samples of fecal microbes every 6 hours from mice on a normal laboratory schedule, with 12 hours of daylight and ad libitum feeding. The authors found a significant ($P < .5$) fluctuation across the circadian cycle in the abundances of more than 15% of the types of bacteria including Clostridiales, Lactobacillales, and Bacteridales. Metagenomic sequencing showed that at night, when mice are typically awake, genes involved in energy metabolism, DNA repair, and cell growth were particularly active. During the light phase, when the mice were more likely to be asleep, their microbes were engaged in more maintenance functions, including detoxification and flagellar assembly.

These day-to-night patterns were absent in mice missing the *Per1* and *Per2* genes, which are necessary for maintaining circadian rhythms. Fecal samples from these mice showed random, rather than rhythmic, fluctuations in both abundance of types of bacteria and the genes they expressed, indicating that the fluctuations are the result of circadian cycles.

Because the microbes are not directly exposed to light and dark, the researchers suspected the fluctuations were caused by the difference in feeding time. The clock-deficient mice ate continuously during the night and day, but when their food was restricted to just daytime or nighttime, they exhibited the same oscillations in their microbiome as the wild-type mice.

When microbes from either clock-deficient or normal mice were transplanted into germ-free mice kept under normal conditions, the recipients showed normal fluctuations in their microbes again. This, write the investigators, shows that "microbiota rhythmicity is a flexible process that can be lost or regained in response to changed feeding behaviors."

Jet Lag Leads to Obesity in Mice

The rhythmic patterns were also disrupted in a mouse model of jet lag. The rodents' schedules were shifted by 8 hours and then shifted back to normal after 3 days to simulate a flight between time zones 8 hours apart, a pattern that is also similar to what many shift workers experience.

After 6 weeks of repeatedly shifting schedules, jet-lagged mice showed increased weight gain and glucose intolerance, even though their overall food intake was similar to that of control mice. The effect was seen on both high-fat rodent chow (60% of calories from fat) and regular chow. Administering antibiotics to the jet-lagged mice eliminated the symptoms of obesity and glucose intolerance. When fecal microbes from the jet-lagged mice were transplanted to germ-free mice, the recipients showed weight gain and glucose intolerance.

Similar Microbe Changes in Jet-Lagged Humans

The researchers tested two humans, taking fecal samples 1 day before, 1 day after, and 2 weeks after a flight from the United States to Israel. The microbes in these two people showed fluctuations in up to 10% of types of bacteria, with a gene expression pattern similar to what was seen in mice. Samples taken 1 day after the flight showed an increase in Firmicutes, bacteria that have been associated with obesity and metabolic disease in other studies.

In addition, transplanting fecal samples from the jet-lagged humans into germ-free mice resulted in the mice gaining weight and showing impaired glucose tolerance compared with transplants from the same people in a non-jet-lagged state.

The authors have disclosed no relevant financial relationships.

Cell. Published online October 16, 2014.

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Cite this article: Gut Microbiome May Be Key Link Between Jet Lag and Obesity. *Medscape*. Oct 16, 2014.