Metabolic disease and obesity may be caused by abnormal behavior of gut bacteria

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(Medical Xpress)—Taking a single snapshot of all the bacteria that live in a mouse's–or person's–stomach and intestines can capture the health of the organism's digestive system and even their risk of developing immune diseases and cancers. But it might take more than one snapshot to get a full picture, Salk researchers have discovered.

In a healthy, lean mouse, the gut microbiome–the full collection of microbes inside their digestive system–undergoes a complex daily cycle, according to new research. Some bacteria are found at highest levels during the night, for example, while others peak during the day. These fluctuations, however, disappear in obese mice, which could be a contributing factor to metabolic disease.

"Previously, the message was that there are beneficial microbes and there are harmful microbes," says senior study author Satchidananda Panda, an associate professor in Salk's Regulatory Biology Laboratory. "We found that it's more complex than this; different microbes are needed at different times of the day."

In the new work, published December 2, 2014 in the journal *Cell Metabolism*, Panda's group compared the microbiomes of mice fed normal food versus those given high-fat chow. Rather than take one daily measurement of the animals' gut microbes, they measured the populations of microbes every four hours. In the mice on normal diets–who eat during the night and sleep during the day–the researchers saw dramatic fluctuations in the particular genera of bacteria present at

any given time. But in the mice that were on a high-fat diet–and generally eat around the clock, gain weight and develop diabetes–the microbes remained more constant.

The pattern was evident among multiple species of bacteria, including firmicutes, a type of bacteria other scientists have associated with obesity and disease.

"We showed that healthy mice can, in fact, have high firmicute levels during the night when they're eating, but this wanes during the day when they're fasting," says Amir Zarrinpar, a University of California, San Diego gastroenterologist who collaborated with Panda's group. In obese mice, firmicute levels were, indeed, high all the time. The observation suggests that it's not whether or not an organism has high firmicute levels that dictates health, but when or how often those levels peak–and the pattern wasn't just seen among firmicutes.

When the researchers limited the food access of the obese mice so they could only eat during the night, some types of bacteria began fluctuating on a daily basis again–although not as many as seen in the mice on normal, lower-fat diets.

"The fact that we can restore some of these patterns with time-restricted eating shows that the timing of meals–not just what or how much is eaten–really matters to the microbiome," says Zarrinpar. Fluctuations in the levels of bacteria, the researchers went on to show, can in turn cause fluctuations in bile acids–molecules that play key roles in controlling cholesterol levels, fat absorption and metabolism throughout the body. The researchers hypothesized that the flattening out of daily microbes cycles may be contribute to metabolic diseases by changing the daily fluctuations of these molecules.

The observation has immediate implications for basic research, Panda

says. "Whenever anyone does any kind of microbiome research, they now need to pay close attention to what time of day all their experiments are done," he says. But it also has an impact on human clinical studies of probiotics, bacterial mixtures which aim to encourage a healthy balance of microbes within the gut microbiome.

"Just like what times you eat throughout the day shapes your microbiome, what time you take a probiotic might change its effectiveness," Panda explains. "If you're taking a probiotic at a time when those particular microbes aren't favored, it could alter those cycles of bacteria in a negative way. Likewise, if you take it at a time when those microbes are naturally rising, you could help encourage healthy cycling."

Panda's group has a plethora of questions remaining about how and why the bacteria fluctuate over a 24-hour cycle. They'd next like to investigate what factors change within the gut–from pH to immune molecules–in response to a high-fat diet that then alters what bacteria are present at different times.

More information: "Diet and Feeding Pattern Affect the Diurnal Dynamics of the Gut Microbiome." DOI: dx.doi.org/10.1016/j.cmet.2014.11.008

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