

Scientists find high-fat diet disrupts body clock

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Our body's 24-hour internal clock, or circadian clock, regulates the time we go to sleep, wake up and become hungry as well as the daily rhythms of many metabolic functions. The clock -- an ancient molecular machine found in organisms large and small, simple and complex -- properly aligns one's physiology with one's environment.

Now, for the first time, a Northwestern University and Evanston Northwestern Healthcare (ENH) study has shown that overeating alters the core mechanism of the body clock, throwing off the timing of internal signals, including appetite control, critical for good health. Animals on a high-fat diet gained weight and suddenly exhibited a disruption in their circadian clocks, eating extra calories during the time they should have been asleep or at rest.

The study, which will be published in the Nov. 7 issue of the journal *Cell Metabolism*, also shows that changes in metabolic state associated with obesity and diabetes not only affects the circadian rhythms of behavior but also of physiology. Probing beyond the behavioral level, the researchers observed actual changes in genes that encode the clock in the brain and in peripheral tissues (such as fat), resulting in diminished expression of those genes.

These findings close an important loop in studies led by Joe Bass, M.D., assistant professor of medicine and neurobiology and physiology at Northwestern and head of the division of endocrinology and metabolism at ENH, of the relationship between the body clock and metabolism.

Two years ago Bass and his colleagues reported in the journal *Science* that a faulty or misaligned body clock can wreak havoc on the body and its metabolism, increasing the propensity for obesity and diabetes.

Since then, knowing that genetic mutations rarely are the reason for a malfunctioning body clock, Bass has been wondering what could upset the operation of this internal timing device. What are the environmental factors or common influences that might affect the clock and in turn disrupt the sleep/wake cycle?

“Our study was simple -- to determine if food itself can alter the clock,” said Bass, senior author of the paper. “The answer is yes, alterations in feeding affect timing. We found that as an animal on a high-fat diet gains weight it eats at the inappropriate time for its sleep/wake cycle -- all of the excess calories are consumed when the animal should be resting. For a human, that would be like raiding the refrigerator in the middle of the night and binging on junk food.”

The clock-metabolism cycles feed on each other, creating a vicious loop, says Bass. Once weight gain starts, the clock is disrupted, and a disrupted clock exacerbates the original problem, affecting metabolism negatively and increasing the propensity for obesity and diabetes.

“Timing and metabolism evolved together and are almost a conjoined system,” said Bass. “If we perturb the delicate balance between the two, we see deleterious effects.”

The biological clock is central to behavior and tissue physiology. Clocks function in the brain as well as lung, liver, heart and skeletal muscles. They operate on a 24-hour, circadian (Latin for “about a day”) cycle that governs functions like sleeping and waking, rest and activity, fluid balance, body temperature, cardiac output, oxygen consumption and endocrine gland secretion.

In their study, Bass and his team studied mice with the same genetic backgrounds. After feeding them a regular diet for two weeks, they were split into two groups for the remaining six weeks, one kept on a regular diet and the other fed a high-fat diet. After two weeks, those on the high-fat diet showed a spontaneous shift in their normal pattern of activity/eating and resting/sleeping. They began to eat during their typical rest or sleep period (daylight for a mouse). The animals on a regular diet did not exhibit this behavior.

“It’s not just that the animals are eating more at regular meals,” said Bass. “What’s happened is that they actually shift their eating habits so that all excess food intake occurs during their normal rest period.”

In the study’s high-calorie, high-fat diet, 45 percent of calories was contributed by fat. For humans, a diet with no more than 30 percent of calories from fat is recommended.

The entire study was conducted in darkness so that the behavior of the animals simply reflected their internal clock; a normal animal has a very fixed daily period of just less than 24 hours. For animals on a high-fat diet, after two weeks on that diet the animals’ behavior changed: their daily period of sleep/wake was lengthened by a significant amount. This suggests, says Bass, that the central mechanism in the brain that controls the timing of the cycle of activity and rest is affected by a high-fat diet.

“Our findings have implications for human disease,” said Bass. “These basic advances in science can be applied to the studies of common disorders like obesity and diabetes. It is important to understand what happens when diet changes.”

Source: Northwestern University

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