Compound is key coordinator of clock and metabolism

March 19 2009

Our circadian clock, or biological timing system, governs our daily cycles of feeding, activity and sleep. Research using cells has produced a solid portrait of the clock at the genetic and molecular levels, but understanding how those mechanisms contribute to the health and disease of living animals, including humans, has been elusive.

Now researchers at Northwestern University and Washington University School of Medicine, in a new study to be published online March 19 by the journal *Science*, have uncovered a surprising new connection between the circadian clock and metabolism in mammals.

The findings could help researchers better understand the circadian disruptions that often afflict the elderly. The results also offer a new target for the development of therapies for the treatment of metabolic disorders related to circadian disruption, such as those experienced by shift workers or even those whose circadian system is disrupted due to obesity or diabetes.

In a study of laboratory mice, the researchers discovered the circadian clock genes strongly regulate the production of nicotinamide adenine dinucleotide (NAD), a critical cofactor involved in numerous cellular reactions and essential to energy utilization. In turn, NAD regulates the activity of an enzyme called SIRT1, which is a known key regulator of aging, metabolism and longevity.

This discovery -- that NAD and SIRT1 together function as a molecular

"switch" to coordinate the internal clock with metabolic systems -- will help researchers better understand how aging, metabolism and the circadian clock are interconnected in living animals through this intricate molecular pathway.

"This is one of the sought-after links that couples changes with the cellular environment and nutrient state with changes in the internal clock," said Joe Bass, M.D., Ph.D., a co-senior author on the paper and assistant professor of medicine and of neurobiology and physiology at Northwestern.

The researchers also found that levels of NAD oscillate, or move up and down according to the animal's internal clock. This is the first evidence of a "metabolic oscillator," an oscillating factor that is not part of the core clock machinery.

Research out of Bass' lab a few years ago showed a clear link between disruption of the circadian clock with the development of obesity and the metabolic syndrome in mammals. The new findings help explain, in part, the molecular activity underlying those pathologies, says Bass.

The other co-senior author of the *Science* paper is Shin-ichiro Imai, M.D., Ph.D., associate professor of developmental biology at Washington University. The interdisciplinary collaboration joins their areas of expertise to focus on circadian clocks, metabolism and aging. Bass' lab has a physiological focus on pathologies related to clock disruption. Imai's lab studies the molecular connections among NAD, metabolism and aging.

"NAD is an essential nutrient in our bodies that controls the pace of metabolism and drives our daily cycles," said Imai. "If that important compound gets messed up, our daily rhythmic cycle also will get messed up, which can lead to serious disease and affect the aging process. It is

very important to maintain this compound and its pathway."

The researchers studied normal mice and those with disrupted circadian clocks, which resulted in obesity and diabetes. They put the mice in total darkness for 48 hours and measured, in the animals' livers and fat tissue, the levels of NAD as well as nicotinamide phosphoribosyltransferase (NAMPT), a regulator of NAD.

Unexpectedly, the researchers found, in the control animals, the levels fluctuated, or oscillated, according to the animals' internal clocks. (The internal clock's rhythmic cycle is maintained even in darkness.) In the mutant animals, those with disrupted circadian clocks, there was a deficit in the levels. Also, the levels were flat -- they did not move up and down.

"Seeing this striking abnormality in the NAD levels was like discovering the cause of a disease in a patient after running a blood test," said Bass, who is head of the division of endocrinology and metabolism at NorthShore University HealthSystem. "The pathway that controls NAD is tied to the clock at the most intricate level. This shows a direct connection -- changes in the clock influence NAD."

The research team also demonstrated the flip side of this relationship: A deficit of NAD negatively affects the clock. "Perturbing the NAD pathway does affect the clock," said Bass. "It does go in both directions."

"While we know that the circadian clock and metabolism are closely linked, we do not know much about what links these two processes on a molecular level, which is what our lab is interested in solving, said Kathryn Ramsey, a postdoctoral fellow in Bass' lab, a former graduate student in Imai's lab and one of the co-first authors of the paper.

"If we can understand the molecular pathways linking the circadian clock with metabolism, we will be better positioned to uncover new

targets for disease intervention and prevention," said Ramsey.

More information: The Science paper is titled "Circadian Clock Feedback Cycle Through NAMPT-Mediated NAD+ Biosynthesis." In addition to Bass, Ramsey and Imai, other authors are Dana Abrassart, Yumiko Kobayashi, Biliana Marcheva, Hee-Kyung Hong, Jason L. Chong, Ethan D. Buhr and Joseph S. Takahashi, from Northwestern University; Jun Yoshino and Cynthia S. Brace, from Washington University School of Medicine; and Choogon Lee, from Florida State University.

Source: Northwestern University (news : web)