Biochemical link between biological clock and diabetes discovered

September 19 2010

Biologists have found that a key protein that regulates the biological clocks of mammals also regulates glucose production in the liver and that altering the levels of this protein can improve the health of diabetic mice.

Their discovery, detailed in this week's advanced online publication of the journal *Nature Medicine,* provides an entirely new biochemical approach for scientists to develop treatments for obesity and type 2 diabetes. It also raises the interesting possibility that some of the rise in diabetes in the U.S. and other major industrialized countries could be a consequence of disturbances in sleep-wake cycles from our increasingly around-the-clock lifestyles.

"We know that mice that don't have good biological clocks tend to develop diabetes and obesity," said Steve Kay, Dean of the Division of Biological Sciences at UC San Diego and one of the lead authors of the research study. "And we know that mice that have developed diabetes and obesity tend not to have very good biological clocks. This reciprocal relationship between circadian rhythm and the maintenance of a constant supply of glucose in the body had been known for some time. But what we found that's so significant is that a particular biological clock protein, cryptochrome, is actually regulating how the hormone that regulates glucose production in the liver works in a very specific way."

"We used to think that our metabolism was regulated primarily by hormones that are released from the pancreas during fasting or feeding.

This work shows that the biological clock determines how well these hormones work to regulate metabolism," says Marc Montminy, a professor in the Clayton Foundation Laboratories for Peptide Biology at the Salk Institute for Biological Studies. "The study may explain why shift workers, whose biological clocks are often out of kilter, also have a greater risk of developing obesity and insulin resistance."

Cryptochrome was first discovered by scientists as a key protein regulating the biological clocks of plants. It was later found to have the same function in fruit flies and mammals. But its role in regulating glucose production in the liver came as a complete surprise to the UCSD and Salk team, which included scientists from the Genomics Institute of the Novartis Research Foundation in San Diego, the University of Memphis and the Chinese Academy of Sciences in Shanghai.

"What was incredibly surprising is that cryptochrome has a new function that nobody had predicted," said Eric Zhang, the first author of the study and a researcher in Kay's UCSD laboratory. "Until now, cryptochrome had been known as a protein inside the nucleus of mammalian cells that switches genes on and off in a rhythmic way. What we showed was that cryptochrome has a role outside the nucleus as well."

That additional function of cryptochrome in mammalian cells, the scientists discovered, is to regulate a process known as "gluconeogenesis," in which our bodies supply a constant stream of glucose to keep our brain and the rest of our organs and cells functioning. When we're awake and eating, sufficient glucose is supplied to our bloodstream. But when we're asleep or fasting, glucose needs to be synthesized from the glycogen stored in our liver to keep our glucose levels up.

"That is how our energy metabolism evolved to function in concert with our diurnal activity, or in the case of the mice, their nocturnal activity,"

said Kay. "This molecular mechanism involving cryptochrome presumably evolved to coordinate our energy metabolism with our daily activity and feeding levels. So could some instances of diabetes be the result of a faulty circadian clock? And if that's the case, can we find ways of fixing the clock to treat this disease? Such an approach would be a whole new way of thinking about how to develop new treatments for diabetes."

In their study, the scientists found evidence that such an approach would be feasible. "Our experiments show very nicely that modulating cryptochrome levels in the liver of mice can actually give diabetic animals a benefit," Kay added.

The researchers discovered cryptochrome's role in gluconeogenesis while studying how a signaling molecule known as cyclic AMP interacted with the biological clock.

"It had been known for some time now that there was a connection between cyclic AMP signaling and circadian rhythm regulation and that's where we started," said Kay, "by asking the question: How are those two connected?"

Zhang and his UCSD colleagues conducted a series of experiments that found that the production of the next step after cyclic AMP, a protein called Creb, ebbed and flowed rhythmically in the livers of mice. That led the scientists to their initial discovery that cryptochrome was regulating the production of Creb in the liver.

In their studies with fasting and insulin-resistant mice at the Salk Institute, the scientists found that cryptochrome was regulating how the hormone glucagon, which controls gluconeogenesis, works in a very specific way. By controlling the production of cyclic AMP, crytochrome regulates the activity of Creb in the liver. In this way, the production of

glucose in the liver is tied through our daily eating, sleeping and fasting activities through the biological clock.

The scientists say their discovery may open up a whole new area of research into how cryptochrome may be regulating other cell functions outside the nucleus.

"There's a wide role that the biological clock may be playing in influencing other hormones, not just glucagon, that are important for metabolism," said Kay.

In addition, studies on human populations have found links between disturbances in the biological clock, such as shift work and chronic jet lag, and the propensity to develop certain kinds of cancers as well as diabetes. Because of this, the scientists plan to continue their research into cryptochrome, looking for compounds that may enhance or diminish the activity of this critical biological clock protein.

Provided by University of California -- San Diego