July 17, 2012

Surprising Discovery Links Biological Clock to Blood Glucose Regulation in Diabetics

Professor Frank Doyle created a mathematical model for the complex effects of cryptochrome on blood glucose levels

Biologists Steve Kay and Tsuyoshi Hirota at UC San Diego, in collaboration with UC Santa Barbara professor Frank Doyle, uncovered surprising results when they found a biochemical link between the chemicals that regulate circadian rhythm and blood glucose levels. They found that a key protein, cryptochrome, that regulates the biological clocks of plants, insects and mammals also regulates glucose production in the liver--and that altering the levels of this protein could improve the health of people with diabetes.

Their findings are a promising discovery for new diabetes therpeutics based on the chemicals that control our biological clock.

Kay and his collaborators discovered in 2010 that cryptochrome plays a critical role in regulating the internal timing of our cyclical eating patterns, timing our fasting at night with our eating during the day to maintain a steady supply of glucose in our bloodstream. Diabetes is caused by an accumulation of glucose in the blood, which can lead to heart disease, strokes, kidney failure and blindness.

?We found that if we increased cryptochrome levels genetically in the liver we could inhibit the production of gl ucose by the liver,? said Kay. What he and his team found in their most recent discovery was that a much sm aller molecule, dubbed ?KL001," can regulate that activity as well. It slowed down the biological clock by st abilizing the cryptochrome protein?that is, it essentially prevented crypotochrome from being sent to the ce llular garbage can, the proteasomes.

Frank Doyle

Researchers in Kay's lab turned to Chemical Engineering professor Frank Doyle for mathematical modeling to better understand the complexities of circadian rhythm and blood sugar regulation. Doyle's research group at UCSB is acclaimed for current research on an Artificial Pancreas System, in collaboration with the Sansum Diabetes Research Institute and diabetes researchers worldwide. Doyle and his colleagues are experts in control systems biology, or using mathematical modeling to understand very complex biological systems such as insulin and glucose controls and circadian rhythms.

"This is a nice example of the power of systems biology--unraveling networks and mechanisms as a means to important therapeutic discoveries," said Doyle. "The collaboration with Steve Kay is both exciting and unusual in that respect. His team really appreciates the value of computational modeling in this endeavor."
Kay commented that Doyle's model "was essential in allowing us to understand the action of the compound because the biological clock is very complicated. It?s like opening the back of a Rolex and seeing the hundreds of tiny little cogs that are tightly integrated." Based on Doyle's model, the researchers predict that adding KL001 to liver cells should stabilize cryptochrome, and therefore inhibit the production of liver enzymes that stimulate glucose production.

Scientists have long suspected that diabetes and obesity could be linked to chemical imbalances related to the biological clock. Laboratory mice with altered biological clocks, for example, often become obese and develop diabetes.

The team's discovery is detailed in a paper published July 13 in an advance online issue of *Science*.

VIDEO: Understand cryptochrome and why it is linked to blood glucose production .

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