Experimental work proves theory that circadian body clock requires delay to function properly

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For more than 20 years, theoretical mathematical models have predicted that a delay built into a negative feedback system is at the heart of the

molecular mechanism that governs circadian clocks in mammalian cells. Now, the first experimental proof of this theory has been provided by an international research team led by molecular biologists and information scientists from the RIKEN Center for Developmental Biology in Kobe. The demonstration of the feedback delay should lead to a better understanding of how cellular clocks function, and therefore how mammals adjust to the regular daily and seasonal changes in their environment. The work could also open the way to the development of treatments for circadian disorders, such as seasonal affective disorder, jet lag and even bipolar disorder.

Mammals not only show daily rhythms of waking and sleeping, but also body temperature, hormone secretion, and many other biological activities. The master cellular clocks that act as timers for these patterns are found in the suprachiasmatic nucleus of the brain. The molecular mechanism is built around a negative feedback system involving cryptochrome (Cry) genes, which code for proteins that repress their own activation by binding with the products of two other genes Bmal1 and Clock. The whole clock system is orchestrated by the interaction of these proteins with a complex array of promoters and enhancers, genetic sequences that regulate gene activity.

Within these clock-gene regulators are short sequences often known as clock-controlled elements. Different clock-controlled elements bind with the different proteins likely to be prevalent at different times of the day or night. The researchers carefully modified these sequences, and observed the impact on circadian rhythms of cells. They focused their studies in particular on the gene Cry1, and observed how the rhythm of its activity was affected by the modifications of clock-controlled elements within promoters and enhancers.

In addition to revealing a previously unknown clock-controlled element in the Cry1 promoter, the researchers also found that different

combinations of clock-controlled elements led to different lengths of delay in the activation of Cry1. They demonstrated that this delay of Cry1 was required for the circadian clock to function.

Based on these findings, they proposed a simple model of the mammalian circadian clock and now want to construct it using artificial components. “We think further experimental and theoretical analyses of this minimal circuit will lead to a deeper understanding of the mammalian circadian clock,” say team members Rikuhiro Yamada and Maki Ukai-Tadenuma.

More information: Ukai-Tadenuma, M., Yamada, R.G., Xu, H., Ripperger, J.A., Liu, A.C. & Ueda, H.R. Delay in feedback repression by Cryptochrome 1 is required for circadian clock function. *Cell* 144, 268–281(2011). www.cell.com/abstract/S0092-8674(10)01437-6

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