Finding the body clock's molecular reset button

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Credit: Vera Kratochvil/public domain

An international team of scientists has discovered what amounts to a molecular reset button for our internal body clock. Their findings reveal a potential target to treat a range of disorders, from sleep disturbances to other behavioral, cognitive, and metabolic abnormalities, commonly associated with jet lag, shift work and exposure to light at night, as well as with neuropsychiatric conditions such as depression and autism.

In a study published online April 27 in *Nature Neuroscience*, the authors, led by researchers at McGill and Concordia universities in Montreal, report that the body's clock is reset when a phosphate combines with a key protein in the brain. This process, known as phosphorylation, is triggered by light. In effect, light stimulates the synthesis of specific proteins called Period proteins that play a pivotal role in clock resetting, thereby synchronizing the clock's rhythm with daily environmental cycles.

Shedding light on circadian rhythms

"This study is the first to reveal a mechanism that explains how light regulates protein synthesis in the brain, and how this affects the function of the circadian clock," says senior author Nahum Sonenberg, a professor in McGill's Department of Biochemistry.

In order to study the brain clock's mechanism, the researchers mutated the protein known as eIF4E in the brain of a lab mouse so that it could not be phosphorylated. Since all mammals have similar brain clocks, experiments with the mice give an idea of what would happen if the function of this protein were blocked in humans.

Running against the clock

The mice were housed in cages equipped with running wheels. By recording and analyzing the animals' running activity, the scientists were able to study the rhythms of the circadian clock in the mutant mice.

The upshot: the clock of mutant mice responded less efficiently than normal mice to the resetting effect of light. The mutants were unable to synchronize their body clocks to a series of challenging light/dark cycles - for example, 10.5 hours of light followed by 10.5 hours of dark,

instead of the 12-hour cycles to which laboratory mice are usually exposed.

"While we can't predict a timeline for these findings to be translated into clinical use, our study opens a new window to manipulate the functions of the circadian clock," says Ruifeng Cao, a postdoctoral fellow in Dr. Sonenberg's research group and lead author of the study.

For co-author Shimon Amir, professor in Concordia's Department of Psychology, the research could open a path to target the problem at its very source. "Disruption of the circadian rhythm is sometimes unavoidable but it can lead to serious consequences. This research is really about the importance of the circadian rhythm to our general well-being. We've taken an important step towards being able to reset our internal clocks—and improve the health of thousands as a result."

More information: "Light-regulated translational control of circadian behavior by eIF4E phosphorylation," Ruifeng Cao et al, *Nature Neuroscience*, published online April 27, 2015. dx.doi.org/10.1038/nn.4010

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