Shedding light on circadian clock control

The circadian clock is the mechanism that coordinates an organism's internal rhythms with daily changes in the environment. To maintain synchronicity, the clock is continuously reset or entrained by signals from the environment, primarily light. But the molecular basis of clock entrainment is not well understood. A new study directed by Shimon Amir of Concordia University and Nahum Sonenberg of McGill University, both in Montreal, Canada, brings to light the process by which entrainment is controlled at the level of mRNA translation. "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," noted Sonenberg in a press release.

The scientists focused on the protein eIF4E, which has a key role in initiating mRNA translation and can be regulated by phosphorylation. In mice, eIF4E was phosphorylated in the brain region that houses the mammalian master circadian clock. Furthermore, phosphorylation of eIF4E was

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regulated by light and by the circadian clock. The research team then engineered the brains of mice to express a mutant version of eIF4E that could not be phosphorylated. Mice with mutant eIF4E did not respond appropriately to manipulations of the light:dark cycle, which included exposure to constant darkness with occasional light pulses or to altered circadian periods of 21 h, 22 h, 26 h or 27 h (*Nat. Neurosci.* **18**, 855–862; 2015). Finally, they found that translation and expression of the period proteins Per1 and Per2, which facilitate clock entrainment, were dependent on phosphorylation of eIF4E. Taken together, the results show that phosphorylation of eIF4E in response to light and circadian cycling promotes translation of Per1 and Per2 and thus has an essential role in the physiology of the mammalian circadian clock.

Dysregulation of the circadian clock is associated with a range of behavioral, cognitive and metabolic disorders, including sleep disturbances. Such disorders are commonly associated with jet lag and shift work and also occur in some neuropsychiatric conditions like depression and autism. Understanding the molecular processes underlying clock entrainment might lead to new ways of treating these diseases. Amir stated, "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."

Monica Harrington

OPTOGENETIC MODEL OF OPIATE EXPOSURE

Optogenetic techniques incorporate light-sensitive proteins into the membranes of targeted cells and enable researchers to alter cell behavior by stimulating the proteins with light. Many studies have used optogenetics to create neurons that can be activated *in vivo* and on demand by exposure to light from nearby light-emitting diodes (LEDs). This field is still growing, and scientists are finding new ways to employ optogenetic methods to manipulate biological systems in living models.

Researchers lead by Michael Bruchas at the Washington University School of Medicine (St. Louis, MO) recently developed a protein called opto-MOR that combines parts of an opioid receptor protein with light-sensitive protein sequences (*Neuron* **86**, 923–935; 2015). In artificial and *in vitro* settings, opto-MOR is highly sensitive to light and initiates cascading intracellular effects that are typical of opioid receptors.

With this tool in hand, Bruchas and his team prepared a mouse model to test opto-MOR *in vivo*. They developed a viral construct that induces cells to express opto-MOR and infused the construct into parts of the brain that are associated with dopamine release and corresponding behavioral responses. They also embedded LEDs in the brains of the mice, near the sites of viral infusion. By activating the LEDs, the researchers could presumably mimic opiate exposure. "Rather than a drug such as morphine activating an opioid receptor, the light provides the reward," Bruchas summarized in a press release.

To verify this presumption, Bruchas *et al.* designed a conditioning experiment wherein mice received LED stimulation upon entering a specific chamber. Control mice were indifferent to this chamber, but mice with opto-MOR showed either a preference or aversion toward the chamber, depending on which region of the brain had been infused with opto-MOR. These behavioral phenotypes are corroborated by similar behavioral responses that accompany administration of opioid agonists in the same regions of the brain.

The behavioral results suggests that LED stimulation can affect neurons though opto-MOR in much the same way that drugs affect neurons through opiate receptors. In practice, though, drug administration is a very coarse manipulation, and neuroactive compounds can interact with a wide range of non-specific cell types in exposed areas, eliciting undesired side effects. The scientists note that, with more research, technologies like opto-MOR might present a precise alternative for studying neural circuits and perhaps even treating pain with fewer unintended side effects.

Gregory D. Larsen

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