Peripheral clocks don't need the brain's master clock to function correctly

October 30 2014

Circadian clocks regulate functions ranging from alertness and reaction time to body temperature and blood pressure. New research published in the November 2014 issue of *The FASEB Journal* further adds to our understanding of the circadian rhythm by suggesting that the suprachiasmaticus nucleus (SCN) clock, a tiny region of the hypothalamus considered to be the body's "master" timekeeper, is not necessary to align body rhythms with the light-dark cycle. This challenges and disproves the commonly held notion that circadian rhythms were strictly organized in a hierarchical manner, and that light resets the master clock in the SCN, which then coordinates the other, subordinate clocks in peripheral tissues. Several metabolic and psychiatric diseases are associated with circadian rhythm and sleep disturbances, and this research opens the doors toward an improved understanding of these disorders.

"Our study reveals a federal organization of internal clock synchronization with the environment," said Henrik Oster, Ph.D., a researcher involved in the work from the Medical Department at the University of Lübeck in Lübeck, Germany. "This suggests that resetting specific peripheral tissue clocks may be an underestimated target for restoring circadian alignment, and possibly to counteract disorders associated with circadian rhythm disruption."

To make this discovery, Oster and colleagues bred mice in which the molecular circadian clock had been deleted specifically in SCN pacemaker neurons, while leaving clocks in peripheral tissues untouched.

These mice, as well as control mice with intact central and peripheral clocks, were then subjected to different lighting conditions. In a rhythmic light-dark environment, gene expression analysis revealed that both groups displayed rhythmic behavior, glucocorticoid hormone rhythms and clock gene expression rhythms in peripheral tissues such as liver or adrenal. When the mice were subjected to constant darkness conditions, behavioral rhythms in the SCN clock-less mice were immediately lost, while endocrine and molecular rhythms gradually dampened over the course of several days. Control mice retained stable rhythms at all levels throughout the experiment. Results suggest a revised model of circadian entrainment, with the adaptation of the internal clock by external time cue, resulting in a mode of photic entrainment in which light can in parallel reset central and peripheral clocks.

"For a long time, we've thought that the central clock in our brains is necessary to keep the other clocks in our body in time," said Gerald Weissmann, M.D., Editor-in-Chief of *The FASEB Journal*. "And this still correct most of the time in most people. This research is important, however, because it not only shows us what might be going wrong in folks with circadian-related disorders, but also helps us to understand how we can manipulate peripheral clocks to help these people."

More information: Jana Husse, Alexei Leliavski, Anthony H. Tsang, Henrik Oster, and Gregor Eichele. The light-dark cycle controls peripheral rhythmicity in mice with a genetically ablated suprachiasmatic nucleus clock. *FASEB J.* November 2014 28:4950-4960; DOI: 10.1096/fj.14-256594

Provided by Federation of American Societies for Experimental Biology