Infradian oscillation of circadian genes in a mouse model of bipolar disorder

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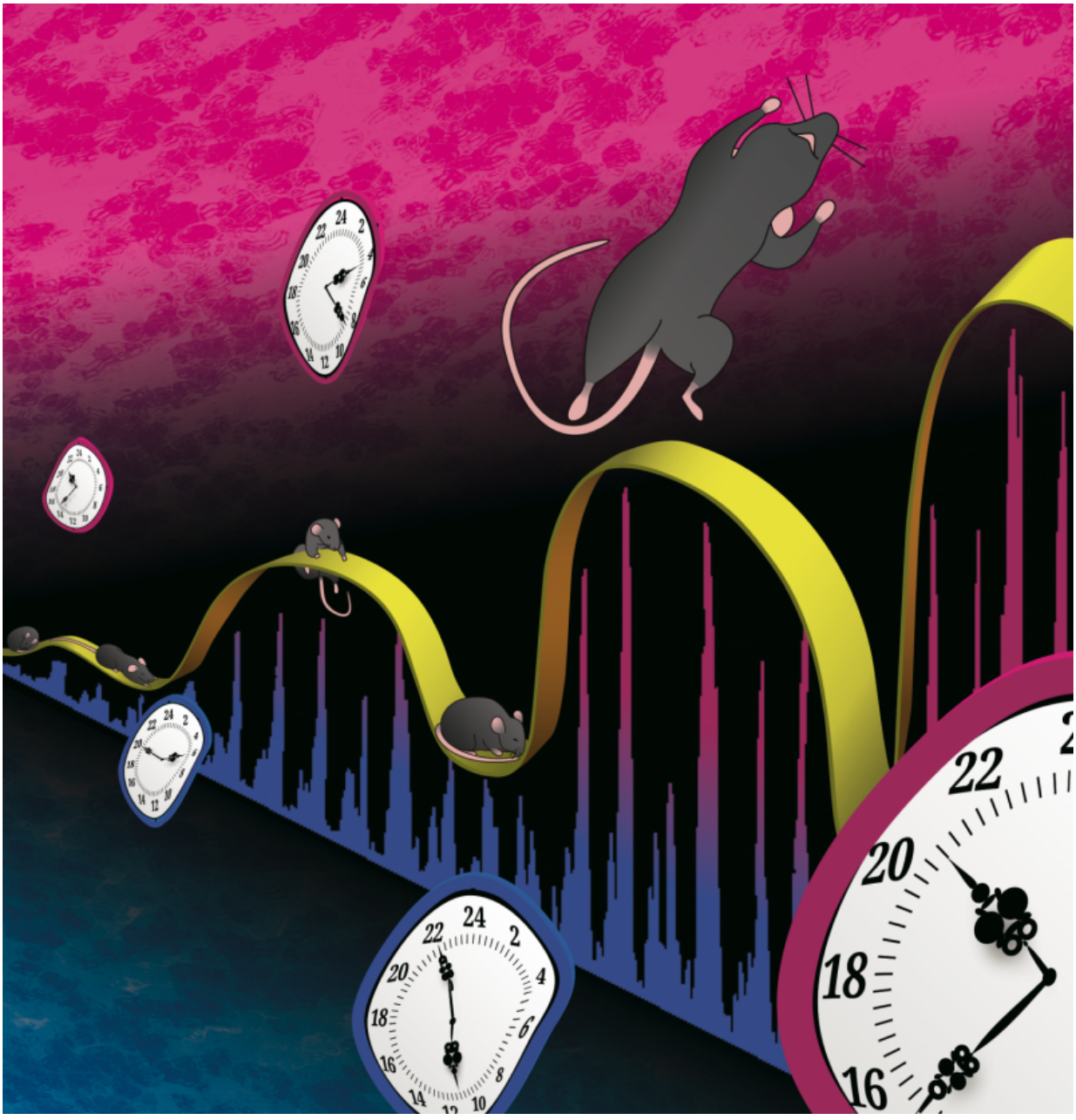

This image illustrates concepts in the press release titled "Infradian oscillation of circadian genes in a mouse model of bipolar disorder". Credit: Hideo Hagihara and Tsuyoshi Miyakawa

Molecular basis of changes in mood and mood-associated behaviors are unknown. Researchers in Japan have succeeded in predicting states of mood-change-like behavior by studying the gene expression patterns in the brain in a bipolar disorder mouse model. They found that expressions of circadian rhythm-associated genes concomitantly change with mood-change-like behaviors in these mice. The current results also provide a novel insight into the molecular basis of bipolar disorder in the brain.

People with bipolar disorder, also known as manic-depressive disorder, experience extreme fluctuations in mood and behavior, which may occur in cycles lasting for days, months, or years. Such changes were first described more than half a century ago, but their molecular basis in the brain has remained unclear. Now, researchers at the Institute for Comprehensive Medical Science, Fujita Health University, and ATR Computational Neuroscience Laboratories in Japan have succeeded in predicting states of mood-change-like behavior by studying the gene expression patterns in the brain in a bipolar disorder mouse model. Interestingly, so-called circadian genes, whose expressions increase and decrease over a 24-hour cycle, are overrepresented in the prediction gene sets, demonstrating an intrinsic link between circadian genes in the brain and mood change-like behavior.

The research appears in the March 29th the journal *Cell Reports*.

Elucidation of the molecular basis of mood changes occurring with an infradian (longer than a day) rhythm has been hampered by the lack of

an animal model that exhibits spontaneous behavioral changes related to the infradian oscillation of mood. In the course of screening over 180 mutant mouse strains with a systematic battery of behavioral tests, Dr. Tsuyoshi Miyakawa and his colleagues found that mice with heterozygous knockout of the alpha-isoform of calcium/calmodulin-dependent protein kinase II (αCaMKII) exhibit behavioral deficits and other brain features consistent with bipolar disorder. Notably, the mutant mice also showed periodic changes in locomotor activity in their home cages with an approximate cycle length of 10-20 days. The changes in locomotor activity are associated with fluctuations of anxiety-like and depression-like behaviors, suggesting that the mutant mice may serve as an animal model showing infradian oscillations of mood substantially similar to those found in patients with bipolar disorder. A recent human study also indicated a genetic association of the αCaMKII gene with bipolar disorder, and decreased expression of αCaMKII has been observed in postmortem brains of patients with bipolar disorder. These findings indicate that αCaMKII mutant mice should serve as a good animal model of bipolar disorder, to elucidate the pathogenesis and pathophysiology of the disorder. In the current study, the researchers used infradian cyclic locomotor activity in the mutant mice as a proxy for mood-associated changes, and examined their molecular basis in the brain by conducting prediction analyses of the gene expression data.

At first, researchers longitudinally monitored locomotor activity of 37 αCaMKII mutant mice by calculating the distance traveled in their cage for over 2 months. Subsequently, researchers dissected the hippocampus, a region thought to be involved in the regulation of mood, from the brain. The sampling of the hippocampus was conducted at the same time of the day (between 1 and 2 p.m.). Gene expression patterns in the hippocampus samples were examined using DNA microarrays that measured the expression levels of over 30,000 genes (transcripts) per sample. Based on the gene expression data, they constructed models for retrospectively predicting locomotor activity of individual mice.

The researchers found that gene expression patterns in the hippocampus accurately predicted whether the mice were in a state of high or low locomotor activity. "This is the first demonstration, to our knowledge, of successful quantitative predictions of the individual behavioral state from gene expression patterns in the brain of a mammal," says Miyakawa. "Gene expression patterns in the hippocampus may retain information about past locomotor activity."

In the current study, prediction analysis of gene expression data was implemented in order to identify the genes that are most useful to determine the state of cyclic changes in locomotor activity. Thus, the researchers examined the list of genes used for the successful prediction of locomotor activity. "To our surprise, the list of 'prediction genes' included significantly higher number of circadian genes, genes that are known to fluctuate according to circadian rhythms. Circadian genes turned out to be also infradian genes, whose expressions go up and down with mood-change-like behaviors in these mice," Miyakawa explains. Researchers also found that levels of cAMP and pCREB, possible upstream regulators of some circadian genes, were correlated with locomotor activity. "The current results provide the evidence for a novel concept that some circadian genes and their regulatory machinery in the brain may be involved in the generation of infradian rhythm behavior," Miyakawa explains.

Furthermore, researchers found that drugs that are used to treat bipolar disorder controlled the locomotor activity and changed hippocampal pCREB expression in the mutant mice. These results support the idea that hippocampal pCREB levels may modulate locomotor activity. "While the work so far has been limited to a mouse model of bipolar disorder, regulating effectively such molecular changes might lead to treatment for the disorder," Miyakawa says.

"It is also of interest whether certain molecular signatures in the samples,

such as blood and cerebrospinal fluid, obtained from living animals can predict past and future locomotor activity. If the successful predictions are confirmed in the mouse model, this strategy may have potential for developing new methods for diagnosis, as well as treatment, of patients with bipolar disorder," Miyakawa says.

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