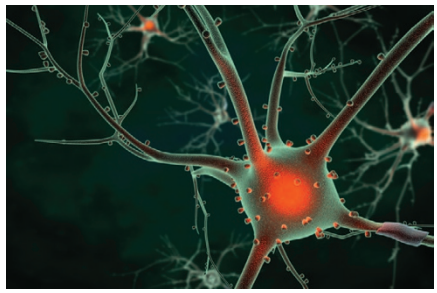
A wake-up call for injured neurons

After suffering a concussion or other traumatic brain injury (TBI), many people (70% or more) experience disturbances in their sleep–wake cycles, such as daytime sleepiness and nighttime insomnia. Such sleep problems can impair attention and memory formation, disrupt quality of life and delay cognitive recovery from TBI. There are currently no proven therapies available to address these sleep disturbances.

Working at University of Pennsylvania (Philadelphia), Miranda Lim and colleagues sought ways to improve these sleep problems by studying a mouse model of mild TBI. Compared with uninjured mice, mice with TBI had a persistent inability to maintain wakefulness and a substantial reduction in activity of orexin-producing neurons when awake (*Sci. Transl. Med.* **5**, 215ra173; 2013). These neurons are involved in maintaining wakefulness in mice and in humans. Orexin has been implicated in narcolepsy and other sleep and arousal disorders in humans, and orexin levels are lower in humans after suffering TBI.

Lim's group next tested whether supplementing the diet with branched-chain amino acids (BCAAs) could restore orexin neuron activity and normalize sleep–wake cycles in mice with TBI. They focused on BCAAs because these compounds are precursors to neurotransmitters and have been shown to increase neural excitability. Although the primary sources of BCAAs in a normal human diet are high-protein foods such as meat and eggs, mice were given BCAAs as a supplement in their drinking water.

In mice with TBI that were treated with BCAAs, the activity level of orexin neurons returned to normal. Treatment with BCAAs partially reversed the sleep–wake disturbances and restored wakefulness in mice. "These results in an animal model provide a proof-of-principle for investigating this dietary intervention as a treatment for TBI patients," said Akiva Cohen, a senior author on the study, in a press release. Lim added, "If further research confirms what this study suggests, we could develop a dietary supplement of these amino acids that could be a viable therapy to help people after a concussion."



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BCAAs have been used to treat humans with other diseases, including liver cirrhosis and bipolar disorder, for periods as long as 2 years without adverse effects. They are clinically well tolerated and have only minor side effects. Therefore, BCAA supplementation may hold promise for treating sleep disturbances associated with TBI and thus improving recovery. As Cohen explained, "If a dietary supplement can improve sleeping and waking patterns as well as cognitive problems, it could help brain-injured patients regain crucial functions."

Monica Harrington

EXCESS FAT REPROGRAMS CIRCADIAN RHYTHMS

The expression of a large number of genes, including those involved in liver metabolism, is regulated by the daily pattern of circadian rhythms. When components of the circadian clock are not functioning properly, normal metabolism is disrupted, resulting in disorders such as diabetes, obesity and high blood pressure.

Now researchers have found that a diet high in fat can interrupt the components necessary for maintaining the liver's circadian rhythms, resulting in widespread changes in metabolism. Paolo Sassone-Corsi and his group at University of California-Irvine fed mice either a high-fat diet (HFD) or normal chow at the same quantities and times for a period of 10 weeks. They measured levels of metabolites every 4 h through the circadian cycle. Of the 306 metabolites they identified, 77% showed an effect of diet on their rhythmicity (*Cell* **155**, 1464–1478; 2013).

Circadian rhythms within cells are controlled by transcriptional feedback loops that produce oscillations in gene expression. Two 'clock' compounds that regulate these feedback loops, CLOCK and BMAL1, are impeded by a HFD, preventing the normal oscillations in expression of metabolites in the liver. Of the transcripts that oscillated in expression, 49.5% were rhythmic only in the normal diet condition but not in the HFD condition.

For many of the metabolites and genes that remained oscillating in the HFD condition, the phase of their oscillations was shifted forward, disrupting the temporal coherence between their cycles and those of their related transcripts. This coherence is important for maintaining metabolic homeostasis.

The HFD also induced oscillations of transcripts and metabolites that usually do not change with the circadian clock: 38 metabolites and 654 genes were newly oscillating exclusively in HFD-fed mice. These effects were mediated both by interfering with the recruitment of CLOCK and BMAL1 to chromatin and by inducing the activity of a transcription factor called PPAR-γ.

The mice fed a HFD became obese, raising the question of whether obesity, and not greater caloric intake, was the cause for the circadian reprogramming of the metabolites. But in another group of mice, a short, 3-day exposure to HFD was enough to initiate the cycling changes even though these mice were a healthy weight.

Yet another group of mice was fed a HFD for 10 weeks followed by 2 weeks of normal chow. The rhythms in these mice normalized after returning to the normal diet, demonstrating that the HFD-induced transcriptional and epigenetic changes are reversible.

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