Team restores memory formation following sleep deprivation in mice

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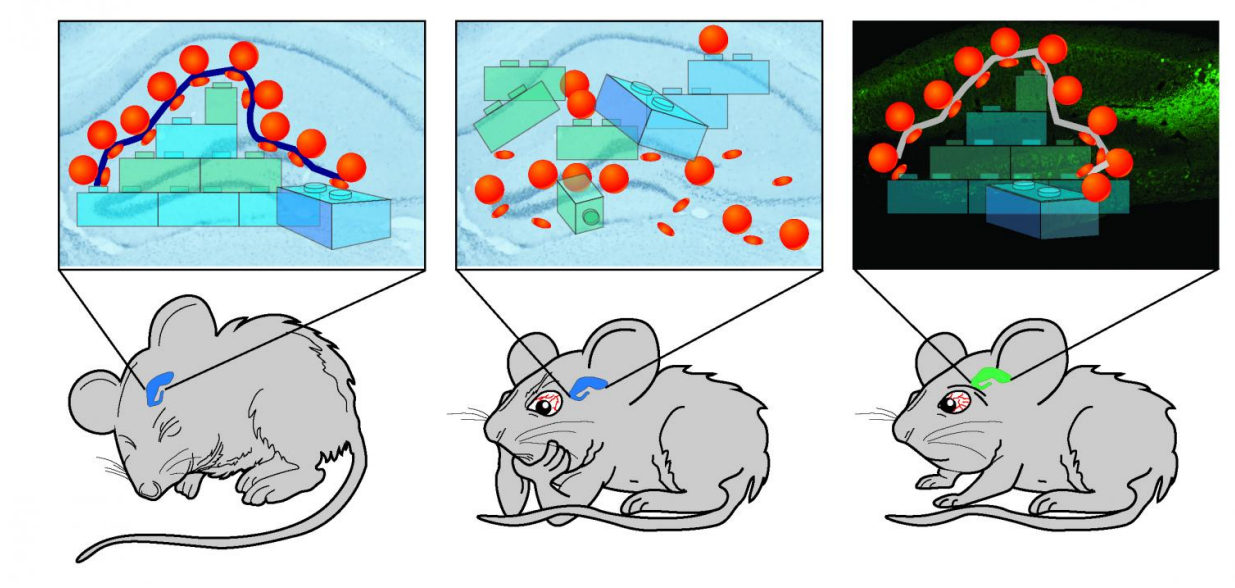

It is thought that sleep facilitates the production of proteins (represented by bricks) required for memory (left). Scientists report that sleep deprivation reduces protein production in the mouse brain (middle). When protein production is increased in the hippocampus region of the brain (green), the negative effect of sleep deprivation on memory was averted (right). Credit: University of Pennsylvania

Pulling an all-nighter may seem like a good way to cram before a test, yet science tells us memory suffers when sleep is sacrificed.

A new study suggests that it doesn't have to.

Researchers from the University of Pennsylvania observed that sleep deprivation is tied to an impairment of protein production in the hippocampus, a brain region thought to be central to memory. By experimentally increasing the expression of a gene involved in regulating protein synthesis in mice, they were able to prevent these deficits.

"While this study isn't immediately translatable to humans, it does lay the groundwork for the identification of the proteins targeted by sleep deprivation." said Ted Abel, Brush Family Professor of Biology and senior author on the paper. "This study also provides a hint about the function of sleep to drive protein synthesis and the strengthening of memories."

"We were able to essentially block the effect of sleep deprivation on memory by manipulating the expression of one gene in the hippocampus," said Jennifer C. Tudor, a postdoctoral researcher in the Department of Biology in Penn's School of Arts & Sciences and the study's lead author. "It turns out that the pathway involved is also incredibly important for cell metabolism, so the connection to energy regulation is potentially very interesting."

The paper was published in *Science Signaling*.

Tudor and Abel's's coauthors on the work included Penn colleagues Emily J. Davis; Lucia Peixoto; Mathieu E. Wimmer; Erik van Tilborg; Alan J. Park; Shane G. Poplawski; Caroline W. Chung and Robbert Havekes. Jiayan Huang of Eli Lilly and Company and Evelina Gatti and Philippe Pierre of the French National Institute of Health and Medical Research also contributed to the study.

Abel's lab has long been interested in the effects of sleep deprivation on

learning and memory and has made key contributions to the field. Earlier work by lab members and others has suggested sleep-dependent memory storage requires protein synthesis.

"There was a lot of correlative data, a lot of suggestive data, but no one had actually shown in vivo that sleep deprivation impairs protein synthesis in the hippocampus," Tudor said.

As a first step in the current study, the research team confirmed this connection between sleep deprivation and protein synthesis using an antibody to a compound called puromycin that tags all newly made proteins. After mice received an injection of this compound, they either were left to sleep or were sleep deprived for five of their normal 12 hours of sleep by gentle handling or tapping their cage.

The sleep-deprived mice had a significantly reduced amount of tagged proteins in their hippocampus compared to mice that got undisturbed rest.

Next, the team wanted to identify a molecular pathway responsible for the reduction in protein synthesis. An earlier investigation had revealed that sleep deprivation had an impact on the expression of genes associated with insulin signaling, including mTOR, which is also involved in protein formation.

Looking at the hippocampi of sleep-deprived mice, the team found reduced levels of mTORC1, a complex of mTOR and other proteins. They also found a reduced amount of phosphorylated 4EBP2, a protein downstream of mTORC1 in the mTOR signaling pathway.

Deducing that the reduction of mTORC1 and 4EBP2 may be involved in the reduced protein synthesis seen after sleep deprivation, the researchers decided to try to use 4EBP2 to prevent that reduction. They

used a viral vector to deliver the 4EBP2 gene to neurons in the hippocampus for three weeks, then subjected mice to the same sleep deprivation test conducted earlier.

They found that not only did the mice expressing 4EBP2 have restored protein synthesis in the hippocampus, but a behavioral test showed that it also prevented memory deficits.

The test, which "exploits the mouse's preference for novelty," says Tudor, involves putting the animals in a box with three different objects, each in a distinct location, and allowing them to explore the set-up. A day later, after either sleeping or being sleep deprived, the mice are returned to the same box, but with one of the objects moved to a new location. If the mice spend more time exploring the moved object, it's a sign that they remembered the old arrangement.

The team found that mice expressing 4EBP2 preferentially explored the displaced object, no matter whether they had gotten a full night's rest or not, showing that the treatment effectively prevented memory deficits due to sleep deprivation.

"What this suggests is that there are proteins that we need in order to create a memory," Tudor said. "As a next step, we're going to identify those proteins that are actively being translated—or not—with sleep deprivation to see if we can catch them in the act and know which ones are most critically affected by sleep deprivation."

Filling in details of how the mTOR pathway, which also plays a role in sensing the body's energy balance, is affected by sleep deprivation may also lead to new research directions for other groups interested in the metabolic consequences of sleep deprivation—like why a poor night's sleep sometimes leads to a case of the munchies.