Forgetfulness might depend on time of day

December 18 2019

Credit: CC0 Public Domain

Can't remember something? Try waiting until later in the day. Researchers have identified a gene in mice that seems to influence memory recall at different times of day and tracked how it causes mice to be more forgetful just before they normally wake up.

"We may have identified the first gene in mice specific to memory retrieval," said Professor Satoshi Kida from the University of Tokyo Department of Applied Biological Chemistry.

Every time you forget something, it could be because you didn't truly learn it, like the name of the person to whom you were just introduced, or it could be because you are not able to recall the information from where it is stored in your brain—like the lyrics of your favorite song slipping your mind.

Many memory researchers study how new memories are made. The biology of forgetting is more complicated to study because of the difficulties of distinguishing between not knowing and not recalling. "We designed a memory test that can differentiate between not learning versus knowing but not being able to remember," said Kida.

The researchers tested the memories of young adult male and female mice. In the "learning," or training phase of the memory tests, the researchers allowed mice to explore a new object for a few minutes. Later, in the "recall" phase of the test, the researchers observed how long the mice touched the object when it was reintroduced. Mice spend less time touching objects that they remember seeing previously. Researchers tested the mice's recall by reintroducing the same object at different times of day.

They did the same experiments with healthy mice and mice without BMAL1, a protein that regulates the expression of many other genes. BMAL1 normally fluctuates between low levels just before waking up and high levels before going to sleep. Mice trained just before they normally woke up and tested just after they normally went to sleep recognized the object. Mice trained at the same time—just before they normally woke up—but tested 24 hours later did not recognize the object.

Healthy mice and mice without BMAL1 had the same pattern of results, but the mice without BMAL1 were even more forgetful just before they normally woke up. Researchers saw the same results when they tested mice on recognizing an object or recognizing another mouse.

Something about the time of day just before they normally wake up, when BMAL1 levels are normally low, causes mice not to be able to recall something they definitely learned and know. According to Kida, the memory research community has previously suspected that the body's circadian clock, responsible for regulating sleep-wake cycles, also affects learning and memory formation. "Now, we have evidence that the circadian clocks are regulating memory recall," said Kida.

The researchers have traced the role of BMAL1 in memory retrieval to a specific area of the brain called the hippocampus. Additionally, they connected normal BMAL1 to activation of dopamine receptors and modification of other small signaling molecules in the brain. "If we can identify ways to boost memory retrieval through this BMAL1 pathway, then we can think about applications to human diseases of memory deficit, like dementia and Alzheimer's disease," said Kida.

However, the purpose of having memory recall abilities that naturally fluctuate depending on the time of day remains a mystery. "We really want to know what is the evolutionary benefit of having naturally impaired memory recall at certain times of day," said Kida.

Mice are naturally nocturnal. When measured in units of time using zeitgeber, the environmental cue of light, mice are usually asleep from Zeitgeber time 1 to 12 and awake from Zeitgeber time 12 to 24. The term "just before normally waking up" refers to Zeitgeber time 10, while the term "just after normally going to sleep" refers to Zeitgeber time 4.

More information: Shunsuke Hasegawa, et al. 18 December 2019.

Hippocampal clock regulates memory retrieval via Dopamine and PKA-induced GluA1 phosphorylation. *Nature Communications*. DOI: 10.1038/s41467-019-13554-y