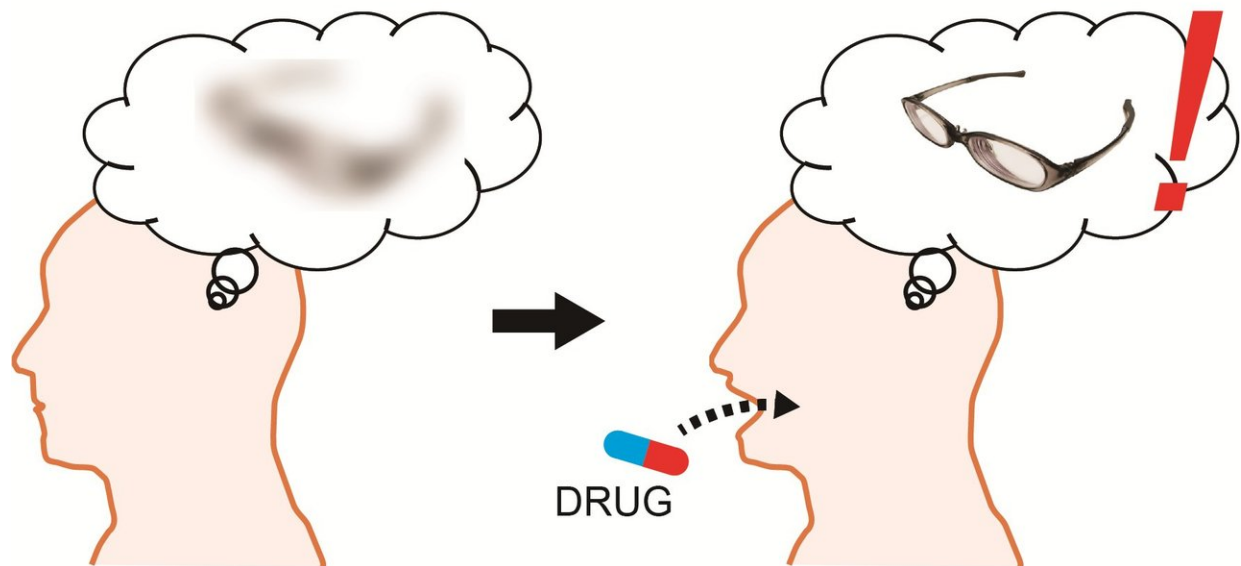


Drug can boost long-term memory of objects

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Researchers at the University of Tokyo led by Professor Yuji Ikegaya studied the effect of histamine on long-term memory. After taking a drug to boost levels of histamine in the brain, adults in their mid-20s had improved long-term memory test scores and mice temporarily had memories that lasted 25 days longer than normal. Credit: Yuji Ikegaya and Hiroshi Nomura CC-BY

Allergy sufferers may use antihistamines to reduce symptoms, but new research reveals that better long-term memory might be possible with pro-histamine treatment. Long-term memory is used to remember anything before 48 hours ago.

During recent studies by researchers in Japan, [histamine](#) improved people's long-term [memory](#) test scores depending on the strength of the original memory, and could temporarily extend [mice](#) memories by as much as 25 days longer than normal. Clarifying the role of histamine in memory may alleviate symptoms of memory disorders such as Alzheimer's disease and other forms of dementia.

Professor Yuji Ikegaya and lecturer Hiroshi Nomura, Ph.D., of the University of Tokyo led a research team that included collaborators at Hokkaido University and Kyoto University in Japan.

A total of 38 men and women in their mid-20s completed memory tests over three days. Participants looked at pictures of familiar objects, like eyeglasses or a wristwatch, and then several days later, were shown some of the same images, as well as some similar and some new photos, and were asked if they had seen the image before.

"In real life, we cannot know what we forgot. This is why we do human memory tests with pictures on a computer screen," said Ikegaya.

Seven or nine days later, participants were given either a placebo or a large dose of a medication that increases the amount of histamine in the brain. The unusually large dose ensured the medication crossed the [blood-brain barrier](#), the body's natural defense that inhibits entry into the brain. The same medication is normally prescribed at lower doses to treat dizziness.

Duality

After taking the drug, participants with poor memories recognized more images correctly, while images that had been difficult to recall became easier for all participants to recognize. However, taking the drug lowered scores of participants with good memories, and images that had been

easier to recall became slightly more difficult for all participants to recollect.

"To any students thinking about using this drug as a study aid, I must warn them to first always protect their health, and second to realize that we have not tested whether this drug helps anyone learn or memorize new things," said Ikegaya.

"Increased histamine helped research participants remember an image they knew once but couldn't remember during a long-term memory word-association test," said Ikegaya.

Researchers suspect that the phenomenon of stochastic resonance, adding white noise to a transmission to boost signal strength, may cause the dual effect of histamine improving long-term memory sometimes but hindering it at other times.

Histamine threshold

Ikegaya suggests memory is a combination of a gradient system and a yes:no or 1:0 digital system. Information might be stored in the brain as a gradient, but nerves do not fire until they are above a particular threshold. Below this threshold is "no" or 0, and we cannot remember. Above this threshold is "yes" or 1, and we can remember.

"You still have the memory, but you can't access it unless it is above a particular threshold," said Ikegaya.

Researchers suspect that the drug raises the histamine gradient to the point that the neurons involved in the latent memory reach the threshold level required to fire a signal and make us remember. However, for memories already over the threshold naturally, extra histamine adds too much noise and excessive nerve signaling hinders recall.

Histamine had no effect on participants' scores on tests unrelated to long-term memory.

Mouse memories

Researchers gave mice two plastic toys, one the mice had seen before and another that was new. Mice prefer to explore a new toy, but after three days, mice forget and treat all toys as new. After receiving a medication that increases histamine in the brain, mice could recognize toys they'd seen as long as 28 days ago.

The long-term memory boost was temporary, though. On day 29, all toys were new again to the mice. Researchers saw similar results with two drugs that increase histamine: thioperamide and betahistine.

Experiments to examine the activity of individual neurons in mouse brains revealed that the drugs increased histamine specifically in a brain region known to be involved in visual perception and memory, called the perirhinal cortex. Moreover, histamine reactivated the same neurons that were active in making the memory.

Bad memories

Improved [long-term memory](#) is not always beneficial, such as for sad or fearful memories, or in disorders such as post-traumatic stress disorder (PTSD). Remembering and forgetting are not simple opposites. Instead, researchers suspect that different brain regions and processes are involved in remembering and forgetting.

"If we have typical memory, then there is a balance between the brain systems for remembering and for forgetting. Too much forgetting or too much remembering is likely an upset of that balance," said Ikegaya.

Future memories

Researchers are currently planning future studies to test how histamine levels might affect memory test results in older adults. Other studies will also examine how histamine might be involved in prospective memory, the "don't forget"-type of memories for the future, such as things we might write on reminder sticky notes to our future selves.

This research published in the journal *Biological Psychiatry* is peer-reviewed and included experimental studies in mice and small-scale randomized control trials in people. The neurotransmitter histamine affects the immune response, memory and acid levels in the stomach. Specialized receptors in different areas of the body regulate the different functions of histamine.

More information: Hiroshi Nomura et al. Central histamine boosts perirhinal cortex activity and restores forgotten object memories. 8 January 2019. *Biological Psychiatry*. DOI: [10.1016/j.biopsych.2018.11.009](https://doi.org/10.1016/j.biopsych.2018.11.009)

Provided by University of Tokyo

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