

# How marijuana makes you forget

Drug affects previously overlooked brain cells that have a crucial role in memory formation.

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Researchers have discovered how marijuana disrupts short-term memory.

The drug impairs users' working memory — the ability to retain and use information over short periods of time. Neuroscientists Giovanni Marsicano of the University of Bordeaux, France, and Xia Zhang of the University of Ottawa Institute of Mental Health Research now show that this common side effect occurs because of a previously unknown signalling mechanism between neurons and non-neuronal cells called astrocytes. Their work is published today in *Cell*<sup>1</sup>.

The star-shaped astrocytes have long been considered nothing more than support cells that protect neurons. "Our study provides compelling evidence that astrocytes control neurons and memory," says Zhang. "The supporting actor has become the leading actor."

The psychoactive ingredient of marijuana is tetrahydrocannabinol (THC). Using microelectrodes implanted into the brains of anaesthetized rats, the researchers found that the compound weakens the connections, or synapses, between neurons in the hippocampus, a structure that is crucial for memory formation.

They repeated these experiments in two types of mice that had been genetically modified to alter their production of CB1 receptors, the molecules that interact with THC in the brain. One mouse strain lacked CB1 receptors in hippocampal neurons that synthesize the neurotransmitter glutamate; the other lacked them in those that synthesize the neurotransmitter GABA.

## A process of elimination

THC weakened the synapses in both types of mouse in the same way as in unmodified strains, so the researchers reasoned that the effects of THC must be mediated by CB1 receptors on astrocytes. Marsicano therefore created a third type of mouse, which lacked the receptor in astrocytes. He found that THC had no effect on their hippocampal synapses.

Another set of experiments, on synapse preparations in Petri dishes, revealed that activation of astrocyte CB1 receptors by THC caused receptors for a compound called AMPA to be removed from the membranes of neurons. The removal and insertion of AMPA receptors have been found to mediate weakening and strengthening of synapses respectively, but it was not previously known that astrocytes can control these processes.

Finally, the researchers tested the three strains of mutant mice with a working-memory task in which they had to remember the location of a submerged platform in a water maze. THC impaired the performance of mice lacking the CB1 receptor in neurons that synthesize glutamate and GABA, but not those lacking the receptor in astrocytes.

"It's always difficult to extrapolate from rodents to humans," says Marsicano, "but marijuana impairs working memory in both species, so I expect that similar mechanisms are involved."

## Cause and effect

Ben Whalley, a pharmacologist at the University of Reading, UK, says that the work demonstrates an exciting causal link between astrocyte signalling and cognitive function. "It'll be fascinating to investigate their consequences for endogenous cannabinoid signalling in normal brain function and in pathological states," he adds.



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Understanding how marijuana impairs memory could help researchers to create drugs that have the same therapeutic benefits but fewer side effects.

Marsicano says that the findings could eventually lead to THC-related drugs that specifically target CB1 receptors expressed by neurons and not astrocytes. Such compounds might have therapeutic effects, for example as painkillers, without affecting the function of working memory.

“But,” cautions Whalley, “we still haven’t separated out the different effects of neuronal and astrocyte CB1 receptors, so the jury’s still out on the potential therapeutic effects of targeting the neuronal receptors.”

In the meantime, there may be a far simpler way of minimizing the unwanted side effects of medicinal marijuana.

A study<sup>2</sup> published in 2010 showed that people who smoke strains of marijuana containing high concentrations of an ingredient called cannabidiol do not experience memory impairments. These strains may be the best ones to harness for medicinal purposes.

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## References

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2. Morgan, C. J. A., Schafer, G., Freeman, T. P. & Curran, H. V. *Br. J. Psychiatry* **197**, 285–290 (2010).