NATURE | NEWS

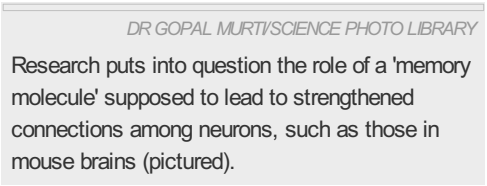
Memory molecule dethroned

Two studies refute an enzyme's essential role in remembering and forgetting.

Ed Yong

02 January 2013 | Corrected: 04 January 2013

For years, a particular protein has been cast as a lynchpin of long-term memory. Inhibiting this enzyme could erase old memories, whereas adding it could strengthen faded ones[1–3]. But two independent groups of US scientists have now seriously challenged the role of this 'memory molecule' by developing mice that completely lack it — and showing that these mice have no detectable memory problems. Their results are published today in *Nature*[4,5].



DR GOPAL MURTI/SCIENCE PHOTO LIBRARY

Research puts into question the role of a 'memory molecule' supposed to lead to strengthened connections among neurons, such as those in mouse brains (pictured).

The excitement around the enzyme, called protein kinase M-ζ (PKM-ζ), started building in 2006, when Todd Sacktor at the SUNY Downstate Medical Center in New York City wiped out established spatial memories in rats. He did so by injecting their brains with ZIP, a small peptide that is meant to block the enzyme[1].

Other teams obtained similar results, erasing different types of memory by injecting ZIP into various brain regions in rodents, flies and sea slugs. And in 2011, Sacktor did the opposite: he strengthened rats' memory of unpleasant tastes by injecting their brains with viruses carrying extra copies of PKM-ζ[3].

Memory surprise

These fascinating studies suggested that long-term memory, rather than being static and stable, is surprisingly fragile, and depends on the continuous activity of a single enzyme.

Richard Huganir of Johns Hopkins University in Baltimore, Maryland, was intrigued by these results, but was concerned that much of the data depended on the actions of ZIP. He and his collaborators took a different route, by deleting two genes — one for PKM-ζ and one for a related protein called PKC-ζ — in embryonic mice[4]. Working independently, Robert Messing and colleagues at the University of California, San Francisco, created similar mice[5].

Neither group of mice showed any memory problems. Messing's animals formed persistent memories for fears, objects, places and movements across a battery of behavioral tests. And Huganir's mice showed normal levels of long-term potentiation — the strengthening of synapses between two neurons that is thought to underlie learning and memory.

"Our study pretty conclusively says that PKM-ζ does not regulate memory," says Huganir. "We were quite surprised." Even more surprisingly, both teams found that ZIP could still disrupt established memories in their mice, despite their lack of PKM-ζ.

"Our study doesn't rule out the possibility that PKM-ζ may play a role in some forms of memory, but it is not the essential master regulator of memory that the current literature suggests it to be," says Lenora Volk, a member of Huganir's team.

But Sacktor argues that the results are "not too surprising" because a different gene might have compensated for the loss, as routinely happens in mice that have had some genes deleted. He suspects that related proteins like PKM-ι or PKM-λ may be involved. "I think the future will be to try to find the back-up mechanisms for memory."

Alternative pathways

However, Huganir's team also created mice whose PKM-ζ gene could be deleted at will by giving them a specific drug. This allowed the researchers to deplete the enzyme during adulthood, after mice had grown up with normal levels. The animals still showed normal long-term potentiation.

"These results do not show that PKM-ζ is unimportant," says Lynn Nadel, a cognitive scientist at the University of Arizona in Tucson. "But they show that the situation is complicated—surprise!—and that there are multiple possible pathways involved."

These other pathways are still a mystery. Without PKM-ζ, “there are not many compelling alternatives for how long-term memory is maintained,” says Huganir. His team is now trying to explore other mechanisms by identifying ZIP’s true targets. “The mechanisms underlying the maintenance of long-term memory will be one of the more exciting areas of neuroscience research for many years to come,” he says.

Nature | doi:10.1038/nature.2013.12139

Corrections

Corrected: This article originally said that excitement over the PKM-ζ protein began with a paper in *Science* in 2007. In fact, the increasing interest began with a paper from Todd Sacktor's lab in 2006. The text has now been corrected to reflect this and the 2006 reference has been added.

References

1. Pastalkova, E. *et al*. *Science* **313**, 1141–1144 (2006).
2. Shema, R., Sacktor, T. C. & Dudai, Y. *Science* **317**, 951–953 (2007).
3. Shema, R. *et al*. *Science* **331**, 1207-1210 (2011).
4. Volk, L. J., Bachman, J. L., Johnson, R., Yu, Y. & Huganir, R. L. *Nature* http://dx.doi.org/10.1038/nature11802 (2013).
5. Lee, A. M. *et al*. *Nature* http://dx.doi.org/10.1038/nature11803 (2013).