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New study refutes accepted model of memory formation

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A study by Johns Hopkins researchers has shown that a widely accepted model of long-term memory formation—that it hinges on a single enzyme in the brain—is flawed. The new study, published in the Jan. 2 issue of *Nature*, found that mice lacking the enzyme that purportedly builds memory were in fact still able to form long-term memories as well as normal mice could.

"The prevailing theory is that when you learn something, you strengthen connections between your brain cells called synapses," explains Richard Huganir, Ph.D., a professor and director of the Johns Hopkins University School of Medicine's Department of Neuroscience. "The question is, how exactly does this strengthening happen?"

A research group at SUNY Downstate, led by Todd Sacktor, Ph.D., has suggested that key to the process is an enzyme they discovered, known as PKM-zeta. In 2006, Sacktor's group made waves when it created a molecule that seemed to block the action of PKM-zeta—and only PKM-zeta. When the molecule, dubbed ZIP, was given to mice, it erased existing long-term memories. The molecule caught the attention of reporters and bloggers, who mused on the social and ethical implications of memory erasure.

But for researchers, ZIP was exciting primarily as a means for studying PKM-zeta. "Since 2006, many papers have been published on PKM-zeta and ZIP, but no one knew what PKM-zeta was acting on," says Lenora Volk, Ph.D., a member of Huganir's team. "We thought that learning the

enzyme's target could tell us a lot about how memories are stored and maintained."

For the current study, Volk and fellow team member Julia Bachman made mice that lacked working PKM-zeta, so-called genetic "knockouts." The goal was to compare the synapses of the modified mice with those of normal mice, and find clues about how the enzyme works.

But, says Volk, "what we got was not at all what we expected. We thought the strengthening capacity of the synapses would be impaired, but it wasn't." The brains of the mice without PKM-zeta were indistinguishable from those of other mice, she says. Additionally, the synapses of the PKM-zeta-less mice responded to the memory-erasing ZIP molecule just as the synapses of normal mice do.

The team then considered whether, in the absence of PKM-zeta, the mouse brains had honed a substitute synapse-building pathway, much in the way that a blind person learns to glean more information from her other senses. So the researchers made mice whose PKM-zeta genes functioned normally until they were given a drug that would suddenly shut the gene down. This allowed them to study PKM-zeta-less adult mice that had had no opportunity to develop a way around the loss of the gene. Still, the synapses of the so-called conditional knockout mice responded to stimuli just as synapses in normal mice did.

What this means, the researchers say, is that PKM-zeta is not the key long-term memory molecule previous studies had suggested, although it may have some role in memory. "We don't know what this ZIP peptide is really acting on," says Volk. "Finding out what its target is will be quite important, because then we can begin to understand at the molecular level how synapses strengthen and how memories form in response to stimuli."

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